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Review Article

The Potentiality of BRCA as a Chemo-Predictor: A Literature Review

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Abstract

The recent studies have been focused for the breast cancer patients to evaluate the relationship between BRCA1 expression and the clinical outcome of chemotherapy (targeting BRCA as a chemo- predictor). Till date, ER, PR and Her2/neu represented as a molecular biomarker which is routinely being used for the treatment strategies for BC patients. Over the last few years, BRCA has been considerably marked as a novel potential biomarker which has been accumulated from several clinical data. Our aim of this study is to review the role of BRCA as a predictive biomarker to spot the chemotherapy response as well as to link the association between BRCA1 deficiency which leads to cancer cell death and the basal- like phenotype. This review is based on the association of literature review which might be helpful to fulfil the lacuna between mutations in BRCA and the chemo-predictive treatment by BRCA as a chemo- predictor to interpret whether BRCA is a predictive factor or a prognostic factor to the clinical outcome with chemotherapy.

INTRODUCTION

The most common cancer in women as a global facet is the "Breast cancer" [1]. Worldwide search has helped to focus on some specific populations who are at risk for developing malignancies for germline mutations within breast and ovarian cancer susceptible genes. Genetic, environmental and hormonal elements are the risk factors included for BC. The genetic risk factors contribute of all BC cases among which90%-95% result from somatic mutation [2] and rest about 5%-10% are inherited as a result of germline mutation in autosomal dominant BC susceptible genes, i.e. BRCA1 and BRCA2 [3,4]. Breast cancer, now-a-days is promptly increasing and has touched the level of most commonly occurring cancer, which is highly heterogeneous in nature according to their histological, physiological and molecular status, although phenotypic and genotypic correlation[5] is also considered as per the location of origin. Despite leading cause of cancer death in women, since last decades the mortality rates has declined profoundly improving survival rates worldwide [6]. Estimated incidence for male breast cancer is 1.08 per 100,000 men (rare), among which accounts for mortality rates less than one third of that.

BRCA AND BREAST CANCER

The BRCA1 and BRCA2 (Breast Cancer Genes 1 and 2), Ataxia Telangiectasia mutant gene(ATM), Phosphate and Tensin homology (PTEN) and Tumor Protein (p53) are the gene which increases susceptibility to cancer and are also associated with familial breast cancer. There are several other predisposing genes also involved which are less frequent but to lesser extent [3,4].

The BRCA1 gene was first identified by linkage analysis [7,8] and subsequently by positional cloning [9,10] and was mapped to chromosome 17q. This gene entails 22 exons coding for a protein which is about 1863 amino acids. The reason for familial breast cancer is the mutations in the BRCA1 gene on 17q21 in half of the female breast cancer patients [11]. Out of 80%-90% of the families there are two or more cases of early onset of breast cancer with a carrier of BRCA1 mutations and genetic predispositions with such carrier are thought to be responsible for 5% - 10 % of all female breast cancer patients [12]. BRCA genes there is no hot spot region more than several recurrent mutations have been reported in several regions. The 5382insC mutation of BRCA1

has been extensively reported by Chakraborty et al. 2013, Castilla et al. 1994, Friedmn et al. 1994, [3,13,14]. This mutation has been originated in the Baltic region during the medieval period (38 generations ago) was reported by Susan L. Neuhausen, et al., in 1996 [15]. It may also significantly increase the risk of prostate cancer in men. Hence, it increases a risk for breast cancer in men.

Another breast cancer susceptibility gene, BRCA2, which is located on chromosome 13q12-q13, also confers a high incidence of breast cancer but, unlike BRCA1, it does not confer a substantially elevated risk of ovarian cancer. Most (though not all) cases of inherited breast cancer in women accounts for BRCA1 and BRCA2 mutations. These mutations are known to be associated with an increased risk for ovarian cancer also. BRCA mutations in men increase the risk for breast cancer and may also increase the prostate cancer risk (www.cancer.gov). BRCA1 and BRCA2 encode protein that is involved in DNA damage repairing, which virtually affects all the cells. Many unique mutations of these two genes have been detected in the germ line of individuals with a breast and ovarian cancer since after BRCA1 and BRCA2 were cloned [9,16]. In an estimated pedigree, female carriers of BRCA mutations are at high risk having 80-90% lifetime risk of breast cancer and a 40-50% lifetime risk of ovarian cancer [15]. Children born from a carrier parents (either of the one parent) have a 50% chance of inheriting the mutation. Therefore, even though men who are carriers face less of a cancer risk than women who are carriers, but both can pass on the mutations to their children.

Mutations in BRCA gene have been linked to various sub-types of breast cancer, i.e. familial which accounts for 15-20 %, hereditary for 5-10 % and sporadic accounting for 70- 75 % which is the most common one [17]. Mutations occur in BRCA1 and BRCA2 gene because of its improper functioning or abnormality in it. Hence, people with BRCA1 & 2 carriers have an estimated lifetime risk for both breast cancer (between 60% and 85%) and ovarian cancer (between 26% and 54%) and between 10 %- 23 % for BRCA gene alone. Overall, women carrying BRCA1 mutation have about 80% and BRCA2 mutation carrying women have likely 85% of probable lifetime risk for developing breast cancer [18,19]. Though, the mechanism of BRCA gene is yet to understand completely but it plays certain key roles in maintaining important cellular pathways like DNA damage response, transcription, genetic integrity, control cell cycle checkpoints, cell division process etc [20]. BRCA1 is a tumour suppressor genes and it is located on 17q21 chromosome which encodes 1863 as a primary product of protein residue, which is also called as p220. Whereas, BRCA2 is also a tumor suppressor gene but it is located on 13q chromosome which encodes a protein of 3418 residue [21]. Although, BRCA1 and BRCA2 both carries almost the same genetic alteration, having complete penetrance. Amongst which mutation in BRCA1 is associated with two targeting organ i.e. breast cancer vs. brain cancer along with neoplastic behaviours i.e. malignant vs. benign form, which is mostly observed at an early age of onset.

Previous study reported that there is another sub-type of cancer i.e. TNBC (Triple Negative Breast Cancer) which is associated with Her-2 and this form of cancer can be characterized by the lack of ER, PR and Her-2 expression [22]. Because of well described characteristics of a BRCA1 associated breast cancer it is called as BRCA ness includes hormone receptor negativity, high grade and basal phenotype [23] and hence these characteristics can also be seen in sporadic breast cancers as it includes BRCA1 associated breast cancers displaying the basal like molecular subtypes of about eighty percent [24-27]. This association with basal like breast cancer involving dysfunction of BRCA1 pathway through non-mutational means and therefore BRCA1- directed therapeutic approaches may be effective in sporadic triple negative breast cancer [28,29]. Breast cancer patients detected with TNBC cannot be treated with any one kind of chemotherapy; these patients require combinational chemo-drugs to target. But its poignant to articulate that it have poor prognosis, as it remains a clinical challenge and are more common among the women with BRCA1 mutations [30] and because of its aggressiveness and poor prognosis effects, it lacks effective therapeutic options [31], still in its infancy for therapeutic options, since clinically it is the most aggressive form of cancer compared to other types like luminal A and B molecular subtypes [32]. An extensive search is needed to be done to find the entity which drives this form of breast cancer subtype, as for the failure or ineffectiveness of the usual anti-endocrine and anti-HER2 targeted therapies as well as the traditional cytotoxic chemotherapy which also seems to be insufficient [33].

This review has been laid down to emphasize the importance of mutation in this gene which will help in genetic counselling and preventive chemotherapy, naming BRCA as a 'chemo-predictor'.

MOLECULAR MARKER USED FOR TREATMENT NOW-A-DAYS

Molecular markers are the biological markers, also known as 'Biomarkers' which identifies distinct sub-groups of breast cancers and is biologically associated and reproducible. These markers can be used as a biological tool in cancer patients for clinical management, assisting in diagnostic procedures, to identify different stages of tumor, evaluating therapeutic response for different dose or dosage response, detection of relapsing and metastasis, prognosis [34] and the development of any new drug treatment way out [35]. Biomarkers are best known when it shows low toxicity with high therapeutic value which could identify the tumor behaviour in a well intervened manner. It has been identified that gene expression profiling is closely related to the molecular behaviour of the tumor which could provide a new therapeutic prognostic tool for molecular diagnosis [36]. It has already been reported that ER, PR and Her-2 are the predictive markers which helps in the identification of high- risk phenotype and for the most proficient therapies selected [37]. In order to understand the gene expression profiling, one have to apprehend the molecular technologies used for generating DNA, RNA, various signalling pathways, epigenetics, protein and metabolic potential that underlies in order to make appropriate treatment decisions.

There are few biomarkers which are well established and have therapeutic effects and prognostic options like Hormone Receptor (HR), expressing proteins both in epithelium and stroma of the breast, mediates cellular effects by binding with circulating hormones [38-40]. Studies reported that ER and PR in

breast cancer are best considered in HR having different clinical, pathological and molecular characteristics in which ER+ and PR+ are the risk factors associated with it and it may also related to the mechanisms of hormonal exposure of breast cancer ER- and PR- and this hormone exposure ought to be independent [41,42] and indicating ER and PR as highly associated with the diagnostic age of the patient as continually increasing.

Her-2 (human epidermal growth factor receptor 2)

Her- 2 gene is also known by quite a few names such as, c-erb-2, cerbB-2, C-erbB-2, HER-2, HER-2/neu, ERBB2, erbB2, erbB2, neu/c-erbB-2/oncogene neu, neu protein, and neu [43]. HER-2 is a transmembrane tyrosine kinase receptor belongs to a family of epidermal growth factor receptors which is structurally related to epidermal growth factor receptor (EGFR), encoded by ERBB2/HER2 oncogene located on chromosome 17q21 [44]. This oncogene which has been considered as a marker of poor prognosis which amplifies in 20to 30% of the breast cancers and it shows resistance to anti-hormonal, cytotoxic therapies, and low overall survival, after its over expression is associated with an aggressive phenotype of tumor cells [40].

Currently, Trastuzumab is a humanized monoclonal antibody and this marker is being directed for the treatment in breast cancer patient with Her-2 positive modalities, targeting against extracellular domains of Her- 2.Trastuzumab is a part of an antitumor antibody which is clinically validated, shows inhibitory efficacy of tumor growth and sensitivity of chemotherapy [45]. Though the inhibitory mechanism of Her- 2 is not yet understood completely, but its antitumor actions work probably by inhibition of receptor- receptor interaction, via endocytosis decreasing receptor by blocking the extracellular domains of cleavage receptor and intern activating ADCC (Antibody-dependent cellular cytotoxicity) [46,47]. After the failure of Trastuzumab, Lapatinib which is a tyrosine kinase inhibitor, has been found with one of its therapeutic strategies targeting Her- 2 protein showing improved efficacy in breast cancer patients. Her- 2 is generally detected in serum of women with benign breast cancer form, and also in primary and metastatic form, which is diagnosed by assessing IHC analysis including FISH (Fluorescent In-situ Hybridization) technique for detection of her- 2 protein and number of gene copy in primary breast tumor tissue [48].

Ki- 67

One of the study reported that Ki-67 is one of the biomarker which has its own potential of clinical as well as pathological response in chemotherapy cycle of early primary systemic therapy which emerges way out for therapeutic options with prognostic factors, however standardization for the integration of this biomarker is needed to be done [49].

Tumor protein p53

The p53 is a tumor suppressor gene involved in several critical pathways including cell cycle arrest, apoptosis, DNA repair and cellular senescence, and these are essential for normal cellular homeostasis and genome integrity maintenance. When TP53 gene gets altered or post-translational modification occurs in p53 protein then it results in alteration of response to cellular stress. Hypotheses concerning etiology and molecular pathogenesis of human cancer are generated by the molecular archaeology of TP53 mutation spectrum [50]. Approximately 30%of the patients display TP53 gene mutation in breast cancer, but fluctuation of the frequency is more than 80% in basal-like to less than 15%in luminal-A subtypes [51]. Early death in node- negative breast cancer was reported by Allred et al. [52], explains that the mutantp53 protein expression was associated with a high tumor proliferation rate and recurrence of early disease. Another study reported which investigated *TP53*mutations in breast tumors from the luminal, basal, and molecular apocrine molecular subgroups, by Dumay et al. [53]. And they found that subgroups differ not only in *TP53* mutation frequency but also in mutation types and consequences. High prevalence of mis sense mutations was detected in luminal tumors and truncating mutations in basal tumors. Whereas, in apocrine molecular tumors, despite high prevalence of insertions/deletions, truncation of p53 was not increased. These observations point to different mutational mechanisms, functional consequences and selective pressures in different subtypes of breast cancer. TP53 gene mutations in-turn results in altered molecular conformation and prolonged protein half-life which leads to nuclear accumulation of altered p53 protein. And this abnormal accumulation was detected by IHC methods and acts as an indirect indicative of mutation in TP53 gene [54]. This nuclear accumulation is an indicator of a poor clinical outcome for breast cancer patients. However, despite its prognostic value, there is still a lack of proper treatment that takes into account for the status of this marker.

CARBOHYDRATE 15-3 AND CARCINOEMBRYONIC ANTIGENS (CA15-3 AND CEA)

Breast cancer is generally not curable once if metastases are detected by classical means such as clinical manifestations of the metastasis, imaging methods, and serum marker assays, which are based on carcinoma antigen 153 (CA 15-3) or carcinoembryonic antigen (CEA) [55]. CA 15-3 in combination with CEA is also considered as a relevant tumor markers in breast cancer [56]. The CEA, a glycoprotein has been considered to be expressed in a vast majority of human colorectal, gastric and pancreatic cancers, and also in breast carcinomas and non-small cell lung carcinomas [57]. In breast cancer, determination of CEA is an indicator of tumor size and nodal involvement. Therefore concentrations of CEA greater than 7.5µg/L are associated with high probability of subclinical metastases [58].

MOLECULAR GENETIC MARKERS

Molecular genetic markers have been proven to be crucial in the diagnosis of single gene disorders. However in various fields especially for cancer care, genetic profiles nowadays have diagnostic, prognostic and therapeutic applications. Based on the application of molecular genetic markers, there are several health care strategies such as molecular diagnosis, prognosis and follow-up of the disease, predictive genetics, pharmacogenomics, molecular-targeted and gene therapy.

A marker which is DNA sequence-based may affect gene expression levels and patterns. For each gene the amount of a transcript is treated as a phenotypic trait, as it reflects changes in the function of a protein more reliably than DNA markers. For exploring functional genetic variation, gene expression profiling

represents a potent tool using RNA molecular genetic markers [59]. Few biological phenomena are quite complex to understand but are crucial though, such as the systematic study of protein structures, posttranslational modifications, protein profiles, protein–protein, protein–nucleic acid, and protein–small molecule interactions, and the spatial and temporal expression of proteins in eukaryotic cells. Proteins are well known as it is essential for maintaining the structure of living cells and their functions. However, the protein profiling technology is still very expensive and time consuming. Therefore, protein-based molecular markers are not yet widely used [60].

RAD51

RAD51, a key component for DNA damage repair which repairs double- strand breakage by HR mechanism which is associated with DNA damage repair. RAD51 nucleoprotein filament is formed after it binds to single and double stranded DNA and hence is responsible during DNA recombination for strand pairing reactions [61,62]. RAD51 gets co- localises with BRCA1 and BRCA2 to the sites of DNA damage mediated by RAD51, and intern activates the HR repair mechanism for double strand breakage [63]. In one of the study [64], it has been reported that RAD51 level lowers in BRCA1 mutated tumors relative to BRCA2 as well as sporadic breast cancer patients. Therefore by inactivating mutations, a BRCA1 dysfunction is caused which appears to deregulate the levels of nuclear RAD51.

RhoC-GTPase

RhoC-GTPase one of the member of R as super family of small guanosine triphosphatases (GTPases) which is involved in cell polarity and facilitate cell motility. This involvement is responsible for actin- myosin contractile filaments into focal adhesion complexes and this entire process happens after the activation of Rho proteins [65- 67]. From one of the research paper [68], report has been exquisitely drawn for the over expression and high motility which characterizes RhoC as a transforming oncogene for human mammary epithelial cells and the finding from this was the over expression of RhoC mRNA in advanced breast cancers by in-situ hybridization. Therefore, by this report it has been hypothesized that RhoC can be considered as a potential marker which would aid to identify breast cancer patients with highly aggressive and motile tumours as well as which could guide therapeutic interventions before the development of metastases. Hence, it has been concluded from their report that RhoC has the high specificity of about 88% in detecting invasive carcinomas with metastatic potential and is also clinically beneficial for the patients with tumor size smaller than 1 cm or small breast carcinomas with metastatic ability [68].

BRCA1 & BRCA2

Apart from that, BRCA1 and BRCA2 are the two breast cancer susceptible genes including majority of the familial breast cancer cases (almost 80%) with one gene hereditary susceptibility for breast and ovarian cancer. These genes have not only risk for breast and ovary but have also increased risk of prostate and pancreatic cancer and however, despite its association with inherited predisposition, somatic disease-causing mutations are extremely rare in BRCA1 or BRCA2 in sporadic breast cancer [69,70]. BRCA is a tumor suppressor gene but because of its loss in wild type allele, it causes to form tumor of heterozygous carriers. Therefore, studies have found that BRCA1 and BRCA2 genes shows variation in geographic and ethnic region group which reflect alterations in genetic characteristics and different lifestyle due to mutation deviations in BRCA genes considering frequency and spectrum. Prediction of BRCA1 or BRCA2 gene mutation from family history which characterizes first degree or second degree relatives and also increased number of affected relatives or bilateral occurrence by diagnosis. Hence BRCA genes can be considered as predictor genes which would help for genetic counselling or making prognostic decisions but still there is a considerable limitation of mutation without such risk factors in breast cancer. Hence definitive predictors are needed to be developed for future prospects in imminent studies. According to few research studies, early diagnosis of breast cancer is already widely available in US and Europe by genetic testing of BRCA1 and BRCA2 genes detection and genetic counselling and this has proved that breast cancer are actually prevented by DNA sequencing of these genes for specific regions and individuals are on safe side by early diagnosis. And if a woman is detected with a risk of breast cancer then those individuals can opt for prophylactic surgery or chemo prevention and among this bilateral mastectomy, though invasive but is at high chances of reducing breast cancer risk approximately 90% with BRCA1/2 mutations.

BRCA AND DNA DAMAGE CHEMOTHERAPY

It is well known that BRCA1 and BRCA2 are the two key genes frolicking crucial roles in DNA damage response in association with DNA double strand breaks involving proteins by non-homologous end joining and recombination respectively [71-73]. BRCA1 is associated with a surveillance complex, a large protein complex which is involved in Nucleotide Excision Repair (NER) [71,74]. DNA damage drugs are directly or indirectly involved in damaging DNA double strand breaks which in turn shows that absence of BRCA1 leads to hypersensitivity of cells to DNA damage- based chemotherapy. BRCA1 containing Ring domain and BRCT domain are both very important in suppressing of formation of breast cancer as well as ovarian cancer in women [75-77]. BRCA1 gene encodes a 220-kDa nuclear protein that responds to DNA damage by participating in cellular pathways which are associated with several proteins and its complex, such as ATM, ATR, DDB2, XPC, GADD45, BACH1, NBS1, BRCA2, RAD50, RAD51, MSH2, MRE11 all together forms a complex for DNA damage repair; transcriptional regulation maintained by a complex of proteins HDAC1, RHA, SWI/SNF, p300, p53, STAT1, few proteins responsible for cell cycle checkpoints regulation which are associated together in a complex are Chk1, RB, Chk2, cyclin B, Wee1, P21, GADD45, 14-3-3σ. BARD1 and BAP1 are associated together for performing ubiquitination. Therefore, all these proteins associated together along with co- transcription factors, majorly functions for tumor suppression and responsible for genomic stability [78].

Scott et al., in 2003 [79], reported that breast cancer formation significantly accelerates if there is a deletion of both BRCA1 and p53. Double stranded DNA damages may be induced by both internal as well as external factors such as oxidative

stress, IR, UV etc. and if these damages are not treated properly then they pass into the daughter cells by accumulating these DNA damages along with DNA replication. Hence, accumulation of these DNA damages leads to genomic instability and causes formation of tumorigenesis. Following this DNA damage, the chromatin associated complex histone H2AX locates close to the sites of the damaged DNA sites which is phosphorylated by ATM and ATR [80,81] and also recruits MDC1 a phospho-module binding mediator and an E3 ubiquitin ligase RNF8 to the sites of damaged DNA [82-85]. RNF8 then functions with E3 ubiquitin to ubiquitination H2A and H2B at the chromatin lesions which in turn regulates the translocation of BRCA1 to damaged DNA sites [81,86,87].

Though p53 is a tumor suppressor gene, few studies have reported that it acts as a predictive biomarker for DNA damage response by increasing the sensitivity to such DNA damaging drugs as well as decreasing the sensitivity to such drugs which was reported by another studies in a contradictory aspect as DNA damaging chemotherapy for breast and ovarian cancer [88-90].

By induction of few chemotherapeutic agents, BRCA1 and BRCA2 genes are involved in cellular responses to DNA damage, as a result reflecting BRCA a functional entity having impact on chemotherapy showing sensitivity [88,91,92]. Few reports revealed that platinum as a chemotherapy in BRCA1 defective cell lines are considered to have the enhanced sensitivity to DNA damaging chemotherapy and also when compared to BRCA competent cell lines [88,93,94]. BRCA1 defective cell lines are found to have relative resistance to microtubule interfering taxanes as chemotherapy [95].

With overall evidence in regard of BRCA sensitivity is that, the BRCA1 has the potentiality to regulate differential sensitivity for different chemotherapy agents, in-vitro. In regard with this, absence of BRCA1 leads to an increased sensitivity to DNA damage chemotherapy whereas, presence of BRCA1 upholds an increased sensitivity to an anti-microtubule agents. Henceforth, it signifies an outcome for clinical breast cancer management because of the use of various chemotherapy agents in different treatment regimens of early as well as metastatic breast cancer [71].

Various results from preclinical and clinical studies, it has been concluded that BRCA1 as a chief factor when loses its functions or ability to perform DNA damage repair through mutation by any means conferring sensitivity to DNA-damaging chemotherapy used commonly in breast cancer as well as ovarian cancer. Therefore, loss of BRCA1 functions proved to be a responsible factor leading to a cancer cell death after DNA damaging treatments. Results of preclinical and clinical studies has been noted from one of the research models that tumours with a loss of BRCA1 expression should results in increased sensitivity to DNA- damaging treatments in sporadic breast cancer patient. However, clinical study reveals that this issue has reported a contradictory result, i.e. an increased in sensitivity [96]. Hence, it can be concluded that between any tumours, the response to DNA- damaging chemotherapy may differ that have reduced BRCA1 function through tumours that have BRCA1 mutation as well as epigenetic silencing.

Progress in women cancers has been made over the past decades for the diagnosis, treatment and prevention of cancer. Poly (ADP-ribose) polymerase inhibitors (PARPis) which have shown a promising activity for breast cancer patients in BRCA1/ BRCA2 mutations as well as ovarian cancer associated with the same mutations, and hence proved to have a wider applications in the treatment of sporadic cancers (mainly high grade serous ovarian cancer) [97,98], DNA repair pathways which are cancer defective such as in prostate, endometrial and pancreatic cancers [99]. A bio mechanism behind PARPis is that it is a highly conserved polymerase enzyme which assists in the maintenance of genomic integrity [100]. It also associates with other enzymes such as PARG, poly (ADP-ribose), glycohydrolase, which is required for hydrolysis and release of single-ADP-ribose moieties [100]. PARPis have also other functions too such as its cleavage and involvement in apoptosis, gene regulation through histone modification and decondensation of DNA for high order chromatin function [101] and DNA damage repair [102]. It signals DNA damage through its ability to recognize and rapidly binds to DNA SSB's [103], it also helps by participating in controlling the telomere length and chromosome stability [104,105].

Few PARPis are in the clinical phase 1/2 trials under investigation and registration as well. According to clinical evidence of the drug, Olaparib is the most studied PARPis showing a promising treatment for BRCA1/2 mutations associated with sporadic breast and ovarian cancers [106] as well as in prostate [107-109] and pancreatic cancers. This drug may also have a therapeutic utility in PTEN- deficient endometrioid endometrial cancer [110], providing evidence that PTEN loss of function considered as a potential predictive biomarker of PARPi responsiveness [111].

BRCA AND CLINICAL RESPONSE IN CHEMOTHERAPY

Clinical studies here address the role of BRCA1 gene in response to chemotherapy. Unfortunately, till date all trials have been backdated in nature and hence no trial has been designed specifically to study the role of BRCA1 in response to chemotherapy. Few studies have grouped both BRCA1 and BRCA2 mutant carriers together, since the genes are not homologous and have different functions, are considered as non- desirable. Although, often complementary, it functions with response to DNA damage [112].

It has been suggested in the current evidence that the overall breast cancer prognosis in BRCA carriers is quite similar to sporadic breast cancers as well as deficiency of BRCA1/2 seems to be predictive of chemo sensitivity. A clinical trialis on-going for metastatic situation which is in Phase II stage and is randomized for testing the sensitivity to platinum-based chemotherapy of BRCA tumours versus taxane-based treatment. A decreased sensitivity has been observed in BRCA1 mutation carriers for spindle poisons, such as one widely used in breast cancer is the taxanes, compared to sporadic patients [113].

BRCA1/2 mutation status which has been studied previously showed association with a worse outcome after invasive breast cancer. [114-116]. The apparent paradox of a preoperative chemotherapy among carriers needs further study, though

it proved to be worthy as an initial response and a worse long term survival. It has been noted that till now no survival studies according to the administration of adjuvant chemotherapy have been stratified. The diagnosis with invasive breast cancer between 1980 and 1995, among a cohort of 292 Ashkenazi Jewish women, Chappuis et al., showed that the overall survival in only among patients who did not receive adjuvant chemotherapy, was significantly worse among BRCA1 mutation carriers compared to non-carriers [117].

BRCA1 mutations were found to be highly sensitive to Anthracycline-based chemotherapy regimens, by Chappuis et al., in 2002. They worked on 38 Ashkenazi Jews patients among which 7 patients were with BRCA1 mutation and 4 with BRCA2 mutations [114]. While in other study Goffin et al., reported in 2003, that if patients did not receive adjuvant chemotherapy or adjuvant hormonal therapy then the BRCA1 mutation carriers had a worse overall survival comparing to the non-carrier patients who also did not receive adjuvant chemotherapy. Therefore the evidence proved that BRCA mutation carriers were more benefited from the adjuvant chemotherapy [118,119].

In 2003, another study by Delaloge et al., confirmed that tumours arising in BRCA1-mutation carriers are more chemosensitive. They investigated in 77 breast tumor patients among which 15 are BRCA1 positive and 5 are BRCA2 positive for the response of neoadjuvant anthracycline- based chemotherapy. A clinical response in 100% of BRCA1 tumours compared with 80% and 63% of BRCA2 and control tumours was observed. A pathological complete response was observed in 53% of BRCA1 patients and only 14% of sporadic controls had a similar response, whereas no BRCA2 patients. Therefore this study suggests that tumours with BRCA1 mutations are more chemosensitive than both BRCA2-mutated and sporadic breast tumours [120].

DISCUSSION

Recent preclinical and clinical studies of various markers are coming up now- a- days to fill the lacuna of the treatment for the breast cancer patients which would give it a new therapeutic option. To address the role of BRCA gene with response to a DNA damage chemotherapy, a widespread research is ongoing but too many questions has been raised in-regard to various markers for its appropriate potentiality to understand the molecular mechanism of the cancer cell death in BC. Few major question arises from this review is that, 'How can we identify the favourable drugs which would really express the potentiality to target these tumours'? 'The second question is to identify these tumors with BRCAness'? Hence, this puts on a big question mark for the researcher so that BRCA could be established as a potential chemo-predictor, to overcome with a grandiose challenge for future prospects.

Insight of BC, there is an exquisite scenario to understand the relationship of genetic as well as epigenetic of this disease progression. Understanding more of the molecular abnormalities involved in BRCA- like tumors, would explore a novel therapeutic strategies as well as drug combinations, which could possibly define a potential predictive biomarkers to improve the clinical outcomes for prognostic approaches.

To bring out the frontiers of therapeutic approaches towards BC is to mainly understand the concept responsible behind BRCAness which explains that the deficiency in other genes which is involved in complex HR pathway confers the sensitivity of PARPis [121]. These crucial findings may raise the possibility that PARPis not only play a major role in BRCA- mutated tumors but is important in tumors with HR- dysfunction as well. This could be identified as a BRCAness which defines the characteristics of sporadic cancers majorly, sharing with BRCA1/BRCA2 cancers suggesting a loss of HR with an underlying defect of DNA repair. Therefore this approach may stands as an ambitious way to identify BRCAness considering the similar phenotypes of sporadic as well as BRCA1/BRCA2 cancers at a functional level. And the major question stands here is to what extent the PARP enzyme could be inhibited which is very important for response towards drug, suggesting in phase2 studies of Olaparib [122-124]. Recent research focus on Receptor activator of nuclear factor (NF)-kB ligand (RANKL) inhibitor will be a promising targetable pathway to prevent BRCA-mutated tumour [125]. Denosumab, a monoclonal RANKL-blocking antibody which was developed to treatment of osteoporosis is now using to treat BRCA mutated breast cancer.

However, our hospital is the tertiary cancer centre which targets to treat patients in a cost- effective way. Therefore, we are looking forward to associate the relationship between the BRCA gene mechanism and the efficacy for the treatment via BRCA as a predictive marker as well as based on chemotherapy or toxal regimens. And hence this association is needed to be explored by the researchers that whether BRCA is an important predictive factor or a prognostic factor to the clinical outcome.

CONCLUSION

Despite the limitations of our study, we confirmed that low/negative BRCA1 expression was associated with better objective response rate (ORR) and longer overall survival (OS) and event-free survival (EFS) in breast cancer patients treated with platinum containing regimen, while high/positive BRCA1 level were associated with better objective response rate in toxal contained regimen. Therefore, BRCA1 might serve as a valuable marker for personal chemotherapy.

The challenge in BRCA1/2-related advanced breast cancer is to develop and support a collaborative mechanism where patients can be identified and entered into randomized trials that test novel therapies such as PARP inhibitors, or mechanistically based chemotherapy, to robustly assess the efficacy relative to standard care, and therefore allow these patients to benefit from these BRCA1/2-focused treatments.

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