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GAVIN PUBLISHERS

Journal of Oncology Research and Therapy

Sookar N, et al. J Oncol Res Ther: JONT-165.

DOI: 10.29011/2574-710X. 000065

Research Article

Factors Influencing Management Strategies for Genetic Mutation Breast Cancers

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Citation: Sookar N, Narinesingh D, Ali J (2018) Factors Influencing Management Strategies for Genetic Mutation Breast Cancers. J Oncol Res Ther: JONT-165. DOI: 10.29011/2574-710X. 000065

Received Date: 20 September, 2018; **Accepted Date:** 26 September, 2018; **Published Date:** 03 October, 2018

Abstract

The highest cancer mortality rate among women in the developing country of Trinidad and Tobago is from breast. We have previously demonstrated that genetic mutation breast cancer risk ranks second highest in the world in this Caribbean island. Widely accepted management strategies for these patients have been described. We report on challenges in applying management strategies in patients with these mutations in our setting and explore possible reasons and solutions to overcome these challenges.

Keywords: BRCA; Hereditary Breast/Ovarian Cancer; National Comprehensive Cancer Network (NCCN); Risk-Reducing Salpingo-Oophorectomy (RRSO); Risk-Reducing Mastectomy (RRM)

Introduction

The annual incidence of breast cancer in Trinidad and Tobago is approximately 57 per 100,000 [1]. This is the highest of any studied Caribbean nation [2-8]. A recent study has shown that genetic mutation breast cancer accounts for more than 10% of all breast cancers in Trinidad and Tobago [9]. Retesting of this cohort of patients including analysis for RAD5IC and CHEK2 yielded a gene mutation breast cancer rate of over 12%. This is the second highest in the world, second to Bahamas at 27% [10]. In comparison, BRCA 1 and 2 gene mutations are responsible for only 3-4% of breast cancers in the US and Canada [11-13]. Women with BRCA1 and BRCA2 mutations have a lifetime risk of developing breast cancer of up to 85% and 62% respectively. There is up to 45% risk of ovarian cancer [8]. As a result, significant emphasis including adherence to management and therapeutic options for these patients and their family members is essential. Established management strategies, according to the National Comprehensive Cancer Network (NCCN) for those with proven mutations are aimed at early detection and management. These include counselling, chemoprevention, surveillance and prophylactic surgery such as bilateral mastectomy and salpingo-oophorectomy. This report highlights challenges in adhering to the recommended guidelines in developing countries such as Trinidad and Tobago while offering some approaches to overcome these challenges.

Methodology

We identify the possible causes for failure of management strategies among 5 patients with BRCA mutations as well as the outcome of these failed strategies. We also review the histories, background, socio economic factors, patient and physician factors as well as other causes of failures and their impact on outcome. From our data base of patients with known genetic mutation breast cancers we identified 2 potentially preventable deaths from breast cancers, 2 patients who are unlikely to pursue standard surveillance strategies because of physician preference and one patient who is deliberately noncompliant. We discuss possible reasons for these occurrences and how best to approach them.

Results

From our database of genetic mutation breast cancer, we identified the following 5 cases that represent different causes for non-adherence to the established management strategies as follows:

Patient 1

She initially presented in April 2011 with right breast carcinoma (invasive ductal adenocarcinoma). She was treated with mastectomy and axillary dissection and her final TNM Staging

was T3N2M0. This was followed by adjuvant radiation and chemotherapy. Her follow-up course appeared being uncomplicated. However, as part of our study cohort she had genetic testing done in 2014 demonstrating BRCA2 mutation. Following this she attended genetic counselling sessions at our centre at which time she was advised about follow-up clinical exams, imaging and because of the aggressivity of her cancer she was advised to consider prophylactic mastectomy on the contralateral breast. She agreed to this but in spite of several reminders, she repeatedly postponed her surgery until she presented to the Emergency department with severe headaches in March 2016. A CT scan of the head showed brain metastasis from which she died 2 months later. All prior CT scans showed no evidence of metastatic disease. This prompted her 2 siblings who were following standard clinical and imaging assessment for breast cancer, to move forward with prophylactic contralateral mastectomy and oophorectomy. They are now stable with no evidence of active breast cancer. A third sibling who was also offered prophylactic surgery remains stable and is followed with 6 monthly clinical examination and MRI's in Tobago. She had initially planned to proceed with prophylactic mastectomy but later decided to continue with close monitoring.

Patient 2

This patient was 28 years of age when she underwent left mastectomy and axillary lymph node clearance for breast carcinoma in June 2012. Final histology from this surgery showed T2N1M0 invasive ductal carcinoma and triple receptor negative. She had genetic testing in 2014 showing BRCA1mutation and had decided to proceed with prophylactic mastectomy but postponed this because of pregnancy. After roughly 1 year of postponement, she underwent prophylactic right mastectomy on January 2016. She was advised to return to us in Trinidad after the surgery, but she continued sporadic follow-up at her home in Tobago until 2017 when she returned to our clinic. Preoperatively, there was no clinical or imaging evidence of breast cancer but her right mastectomy in 2016 showed a 2cm breast carcinoma of ductal origin. Her staging CT Scan at this time demonstrated multiple lung and liver metastasis. She died 8 months later despite chemotherapy.

Patient 3

This patient was aged 22 and pregnant when she presented with left breast invasive carcinoma of ductal origin in January 2012. She underwent left mastectomy and axillary dissection on May 2012, followed by radiotherapy and chemotherapy. In 2014 she had genetic testing and demonstrated BRCA1mutation. She attended genetic counselling session and indicated that she would proceed with contralateral prophylactic mastectomy with reconstruction but cancelled her surgery on 2 occasions and has not been compliant with clinical follow-up or imaging in spite of numerous phone calls. She also refused to give us her siblings' phone contacts indicating that they did not wish to be contacted. We will discuss below possible reasons for non-compliance in these patients.

Patients 4 and 5

Both patients were aged 31 and 42 respectively when they underwent mastectomy for breast carcinoma. They both tested positive for BRCA1 mutation. These patients were informed of the genetic testing results which were given to their referring physician with suggestion of follow-up according to NCCN guidelines, but he indicated he would not pursue this to avoid unnecessary anxiety for the patients who have a "Poor prognosis anyway". We have indicated to the patients that we would be happy to see them, but we have not been approached for appointments. We are considering the best way to deal with these patients without violating the doctor-patient relationship.

Discussion

The emphasis in management of genetic mutation breast cancer is aggressive proactive surveillance to diagnose the cancer at a very early stage and risk reduction strategies including prophylactic surgery. Factors which increase the likelihood of having a genetic mutation related to breast cancer include: multiple cases of early breast cancer/ovarian cancer, bilateral breast cancer, more than one family member with breast/ovarian cancer, male breast cancer, documented BRCA mutations in the family and multiple breast cancer cases across generations.

According to NCCN (2017) guidelines, the management and follow-up strategies for hereditary breast/ovarian cancer syndrome include:

1) Breast awareness starting at age 18.

2) Clinical breast exam, every 6-12 months, starting at age 25.

3) Breast screening as follows:

- Age 25-29, annual breast MRI screening with contrast (or mammogram with consideration of tomosynthesis, only if MRI is unavailable) or individualized based on family history if a breast cancer diagnosis before age 30 is present.
- Age 30-75, annual mammogram with consideration of tomosynthesis and breast MRI screening with contrast.
- Age >75, management should be considered on an individual basis.
- For women with a BRCA pathogenic variant who are treated for breast cancer and have not had a bilateral mastectomy, screening with annual mammogram and breast MRI should continue as described above.

4) Option of Risk-Reducing Mastectomy (RRM) should be discussed and include counselling regarding degree of

protection, reconstruction options, and risks. In addition, the family history and residual breast cancer risk with age and life expectancy should be considered during counselling.

5) The option of Risk-Reducing Salpingo-Oophorectomy (RRSO), typically between ages 35 and 40, and upon completion of child bearing for BRCA1 variant should be discussed. Because ovarian cancer onset in patients with BRCA2 pathogenic variants is an average of 8-10 years later than in patients with BRCA1 pathogenic variants, it is reasonable to delay RRSO for management of ovarian cancer risk until age 40-45 y in patients with BRCA2 pathogenic variants. For ovarian cancer risk, routine screening with transvaginal ultrasound and CA125 are not recommended and is not a reasonable substitute for RRSO in BRCA1 and 2 carriers.

6) There is insufficient evidence to recommend risk reducing medication/chemoprophylaxis (tamoxifen, raloxifene) for BRCA1 mutation but a 50% reduction may result with this chemoprophylaxis in BRCA2 mutation ER positive breast cancers.

7) Counselling should ideally be performed by a trained geneticist or at least a trained clinician who is aware of the risks and is interested in guiding the patients on what signs to look for, to follow imaging guidelines and be aware of the option of preventive surgery.

Resource requirements include supportive services such as gynecologic-oncology, genetic counselling, laboratory and imaging services and a supportive environment. Fortunately, we have a dedicated gyne-oncology service at our site where our genetic mutation cancer cases are given high priority. Our on-site plastic and reconstructive expertise also provides a high calibre of care which is essential for these young patients following mastectomy. The 5 patients described in this report are not typical of our 33 gene mutation breast cancer patients. Indeed, a recent study demonstrated that there was at least a 60% adherence to imaging and clinical guidelines as well as 25% completion of prophylactic surgery with/without reconstruction [14]. However, these 5 cases require our attention in order to guide our approach to ensure adherence to national guidelines.

Low to middle income patients represent a substantial number of our patients. Many of them do not have private medical insurance to cover the cost of imaging such as mammograms and MRI's which are not available on site at our institution.

These imaging modalities are available at other public government funded institutions but the delay in obtaining imaging and reporting is too long for this class of patients. This only adds to the frustration of these patients in trying to follow our recommendations. At our institution, the Ministry of Health has approved a program of funding for gene mutation breast cancers to have timely MRI's in the private institutions on approval by our Director of Health. Funding through our Social services department is possible but limited and very tardy. Ideally, our goal should be to have all our imaging modalities available on site at our breast cancer institution.

We do not have a trained geneticist in our institution and counselling by experienced clinicians as a substitute may not be enough to convince some patients of the dire need for compliance with the guidelines. Infrastructure resources should also include a dedicated nurse navigator to track the patients' journey through their treatment pathways to avoid some of the problems of transfer of care across institutions and between islands. Availability of these resources could have probably made the difference in patients who deliberately choose noncompliance.

As in 2 of our cases, some physicians do have legitimate concerns about providing anxiety provoking information on cancer risk and may decide to withhold this information from their patients. This approach unfortunately denies the patient the opportunity to control their treatment by making their own decisions about their health based on reliable, scientifically based information from their treating physicians. Information on risks should be accompanied by possible approaches to mitigate against these risks to help alleviate the anxiety [15,16]. Also, open consultation with colleagues would help share the physician burden of giving anxiety provoking information about increased cancer risk. In 2 of our cases possible violation of patient doctor confidentiality is a concern that is difficult to address. For example, should the data gathering personnel offer advice to the patient when the personal treating physician chooses not to share that information with the patient? Awareness through education of our physician colleagues is also necessary to avoid some of the issues in the patients which we describe.

Research is also necessary to determine the cause of the inordinately high risk of genetic mutation breast cancer in our population with a view to mount preventive strategies against this devastating disease that afflicts so many of our young females.

Conclusion

Trinidad and Tobago have the second highest risk of genetic mutation breast cancer in the world. Recognised strategies need to be applied. However as outlined, patient issues such as undue delays and noncompliance from lack of education or apprehension can lead to early death. The lack of availability of resources with the current economic climate can also be detrimental. In spite of these elements, we have been successful in securing compliance especially with respect to surveillance and prophylactic surgeries in a large percentage of our patients. These results could be improved by more intense attempts at communication and education which

require infrastructure commitments which can be challenging in low income countries. In spite of offering counselling, imaging, close follow-up and preventive surgery including reconstruction, we were unable to successfully apply standard management strategies for some of our patients for various possible reasons as outlined and with serious consequences including potentially avoidable mortality.

These findings emphasize a great need for patient and physician educational programs, community awareness and appropriately trained genetic counsellors in order to provide much needed care to a very high-risk population as ours. The availability of reconstruction expertise after preventive surgery would encourage compliance. Despite promulgation of information on surveillance strategies for dealing with gene mutation breast cancer patients, a substantial number of patients do not benefit from these strategies, warranting examination of our approach for successfully dealing with this important public health issue particularly in resource poor environments.

Conflicts of Interests Disclosure: The authors declare no conflicts of interest.

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