Management of patients with BRCA1/2-associated breast cancer

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Abstract
BRCA1/2-related breast cancers (BC) can be considered a separate entity compared to sporadic ones. Current knowledge suggests that the overall management is different. Herein, the different topics of management of BRCA1/2-associated BC are considered including cancer genetic counseling, surveillance, chemoprevention, prophylactic surgery, oncological treatment and psychosocial aspects. Cancer genetic counseling is a specific modality for the management of at-risk subjects that foresees a multidisciplinary approach and patients-focused interventions. An integrated multidisciplinary approach in cancer genetic counseling (CGC) is required to support women with high inherited risk of developing hereditary cancers in the complex decisions related to cancer risk management choice. Surveillance for at-risk body sites should be integrated to the conventional oncological follow-up of BC patients and offered to the healthy family members. Chemoprevention and prophylactic surgery are viable options of cancer risk management. Particularly, prophylactic surgery can be considered an effective strategy for BRCA1/2 mutation carriers, because of a significant reduction of BC and ovarian cancer risk. Promising findings concern specific oncological treatment, including also target therapies in this setting. It is necessary that during CGC process the subject at-risk takes an active role, facilitated by a personalized approach and a focus on the patient's emotional state. A patient-centered approach by a bio-psychosocial perspective is needed for the taking charge of at-risk women.

Key words: BRCA1/2 carrier, breast cancer, cancer genetic counseling, chemoprevention, decision-making process, prophylactic surgery, psychosocial aspects, surveillance

Introduction

Breast cancer (BC) is the most commonly diagnosed cancer and the second leading cause of cancer death among women. Overall 5-10% of primary BCs are inherited. About 84% of hereditary BCs derives from BRCA1 and BRCA2 mutations that sustain the Hereditary Breast and/or Ovarian Cancer (HBOC) syndrome [1].

The clinical features that suggest hereditary predisposition to BC include: multiple cases of BC and ovarian cancer (OC) in different generations; an early onset diagnosis of BC and/or OC; two or more primary cancers in the same individual (i.e. bilateral BCs, BC and OC); male BC.

Hundreds of pathogenic mutations or unknown variant sequences (UVS) have been identified in the BRCA genes [2, 3]. Pathogenetic BRCA1/2 mutations have been associated with an increased risk especially of BC and OC and less frequently in different body sites. In Figure 1, penetrance of BRCA1/2 mutations has been reported according to a recent meta-analysis and compared with the risk of BCs and OCs in general population. Carriers of mutations in BRCA1/2 genes have a cumulative risk of about 45-60% of developing BC and an increased risk of developing OC, accounting for about 11-39% [1, 4]. BRCA1-associated BCs are usually high grade, poorly differentiated and infiltrating ductal carcinomas. Atypical medullary carcinomas have also been observed frequently. Tumors frequently show a basal-like phenotype, characterized by estrogen receptor (ER), progesterone receptor (PgR) and HER2 negativity and the expression of basal cytokeratins such as 5, 6 and 14. BRCA2-associated BCs are generally similar to sporadic ones both for phenotype and behaviour [5-7]. BRCA1-related OCs usually are serous and papillary, less frequently endometrioid or clear cell are met [8]. Other cancers that have been shown to be associated with BRCA1/2 mutations include male BC, prostate cancer, pancreatic cancer and melanoma [9, 10].

Herein, the different topics of management of BRCA1/2-as-

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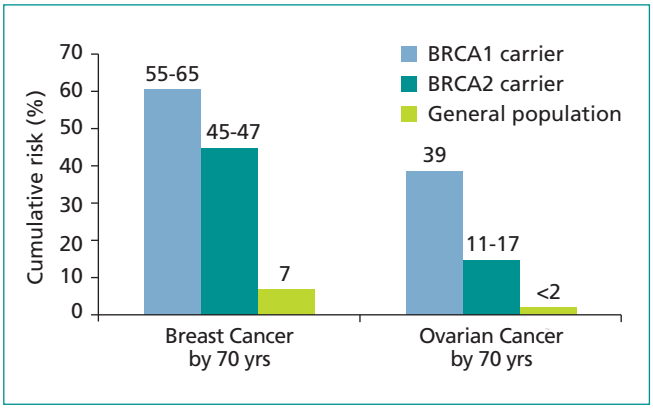

Fig. 1. Penetrance of BRCA1 and BRCA2 mutation, as risk of developing breast and ovarian cancer compared to general population.

sociated BC are considered including cancer genetic counseling (CGC), surveillance, chemoprevention, prophylactic surgery, oncological treatment and psychosocial aspects.

Cancer genetic counseling

In the last years, CGC was included in the work-up of patients with a new diagnosis of BC when clinical criteria are suggestive for a hereditary BC [11]. In Table 1, worldwide clinical criteria are summarized to refer BC patients to CGC. CGC allows to make an adequate diagnosis of the syndrome, to assess the risk and to offer genetic testing according to international guidelines.

Genetic testing should be offered within pre- and post-test counseling by means of good clinical practice in order to evaluate advantage, limits and clinical implications of genetic test [12]. CGC promotes educational process, informed consent and awareness by means of active participation of subjects during the crucial point of CGC, such as the choice of genetic testing and/or the choice of specific measures for risk management (i.e. prophylactic surgery). Moreover, within CGC healthy family members are identified and uptaken because of the benefits from an *ad hoc* preventive program. The multidisciplinary team involved in CGC should provide patient-focused interventions by geneticist, oncologist and psychologist and help the consultants to consider benefits, efficacy, limits and risks related to the various options available for risk management, considering the preferences and psychological profile of women as the crucial point in the decision-making process.

Given the complexity of hereditary cancers issue, the presence of the psychologist in the multidisciplinary team is relevant. The psychologist allows the psychological assessment and provides an emotional containment in all phases of CGC. Moreover, psychological sessions are aimed to empower at-risk subjects, to make informed and aware decision about genetic testing and choices about prevention. The psychologist also provides psychological treatment options for patients that vary from psycho-education, counseling or psychotherapy at an individual, marital and family level [12].

The identification of hereditary BC allows managing patients adequately both for planning the optimal treatment strategy (i.e. surgery, chemotherapy) and for the optimal follow-up because of risk of second primary cancers. The Next Generation Sequencing (NGS) allows inserting genetic test results as integral part of the planning strategy of treatment [13].

Risk-reducing strategies

Surveillance in BRCA1/2-BC patients

Surveillance for at risk body sites should be considered for BRCA1/2-BC patients in addition to conventional oncological follow-up, according to the cancer spectrum typical of HBOC syndrome, namely contralateral breast, ovary/tube and skin [9, 10, 14]. The National Comprehensive Cancer Network (NCCN) proposes a preventive program for BC and OC in females and focuses on prevention in males, particularly BC and prostate cancer, too [11]. Surveillance pro-

Table 1. Clinical criteria to refer patients with breast cancer to cancer genetic counseling

Three or more breast and/or ovarian cancer cases, at least one <50 years
Two breast cancer cases <40 years
Male breast cancer
Early onset breast cancer (≤45 years)
Early onset ovarian, peritoneum or tubes cancer (≤45 years)
Ashkenazi Jew with breast cancer
Young onset bilateral breast cancer
Multiple primary cancers (i.e. breast and ovarian; breast cancer and melanoma)
Medullary carcinoma of the breast
Triple negative phenotype (negative estrogen and progesterone receptors, absence of HER2-neu)

gram includes monthly breast self-examination (BSE), clinical breast examination twice a year and mammograms and magnetic resonance imaging (MRI) of breasts yearly. MRI is involved in surveillance program, especially for young patients in order to maximize sensibility of the diagnostics exams [15, 16].

Transvaginal ultrasound and concurrent CA-125 should be performed every six months in patients who are looking for risk reducing salpingo-oophorectomy [11].

Prostate cancer screening should be recommended to male BC with BRCA1/2 mutations starting at age 40 years [11].

No specific guidelines exist for pancreatic cancer and melanoma. Screening may be individualized based on cancers observed in family, including full-body skin exam in the algorithm of prevention for melanoma [11].

Prophylactic surgery

Prophylactic surgery should be considered in the management of BRCA1/2 mutation carriers patient as a strategy of risk reduction. Risk-reducing surgery with bilateral prophylactic mastectomy (BPM) and reconstruction may be offered to women with a previous diagnosis of BC, if BRCA1/2 mutation carriers. The 10-years actuarial risk of contralateral BC ranges from 25% to 31% [17]. BPM reduces both subsequent BC incidence and cancer-specific mortality by about 90-95% [18]. Graeser et al. reported a high incidence of contralateral BC if first primary BC occurred in BRCA1 mutation carriers ≤40 years. No significant contralateral BC incidence has been showed in BRCA1/2 BC patients >50 years [14].

Bilateral prophylactic salpingo-oophorectomy (BPSO) should be considered in the planning of risk-reducing strategies. It should be practiced between 35-40 years after completing the desire for offspring, because the median age of onset of OC is around 50.8 years (range 30-73 years). BPSO reduces significantly the risk of gynecological cancers of about 50-85% (HR 0.21; 95% CI 0.12–0.39). When performed in premenopausal women, it achieves also a protective effect on the breast, reducing the BC risk of 68% (HR 0.49; 95% CI 0.37–0.65) both in BRCA1 than in BRCA2 carriers. It foresees also a significant impact on mortality for all causes and for BCs and OCs [19]. Recent findings have shown the presence of precancerous lesions, namely serous tubal intraepithelial carcinoma (STIC) inside the tubes in BRCA carriers that suggest the origin of BRCA-related OC from the tubes. The new hypothesis on pathogenesis of OC leads to future and tailored approaches, i.e. salpingectomy as conceivable approach of risk-reducing surgery that allows to protect women from the long-term side effects of premature menopause subsequent to oophorectomy [8, 20].

Chemoprevention

Hormone therapy represents the most utilized adjuvant treatment of early BC. Few data are available on the effects of antiestrogens with respect to BRCA1/2 status. Adjuvant tamoxifen is associated with a reduction of ipsilateral and contralateral BC in BRCA1/2 mutation carriers [21]. Tamoxifen seems to have a positive impact whenever some questions remain open as its efficacy both in BRCA1 and BRCA2 mutation carriers and its role in preventing ER-positive tumors only.

Chemotherapy

Few studies are available about treatment in advanced BC in BRCA1/2 mutation carriers. Data concern the clinical activity of platinum compounds mostly in the neoadjuvant setting [22, 23], and to a lesser degree in advanced disease [24, 25].

Complete pathological response rate were very high in BRCA1 mutation carriers treated with platinum compounds reaching about 83% compared to other regimens that reached a maximum of 22% [22].

Data concerning the advanced setting in BRCA1/2 carriers are lacking. Few data exist for inclusion of platinum in the treatment of metastatic disease in triple negative BC, a putatively BRCA-deficient population [26]. Taking into account the available evidence about the improvement in the outcome in this population, BRCA-associated triple-negative or endocrine-resistant metastatic BC previously treated with an anthracycline and a taxane, platinum-containing regimens should be included in the treatment. All other treatment recommendations are similar to sporadic metastatic BC [27]. In a recent phase II study, the activity of trabectedin has been evaluated in germline BRCA1/2-mutated metastatic BC. Trabectedin monotherapy showed activity in heavily pretreated metastatic BC selected for germline BRCA mutation. These results prompt further evaluation of trabectedin alone or combined with other specific drugs in this indication [28].

Poly (ADP-ribose) polymerase (PARP) inhibitors are being evaluated either alone or in combination with chemotherapy for BRCA-associated tumors, according with the mechanism of synthetic lethality. Recently, two phase II trials provided a positive proof of concept of the efficacy and tolerability of targeted therapy with olaparib in BRCA-mutated tumors. Olaparib provided a response rate of 41% and a progression-free survival of 5.7 months in a heavily pretreated population [29].

Psychological aspects

Cancer risk perception and risk management

Among psychosocial variables associated with worse psychological sequelae for hereditary BC risk, a higher perception

of risk and a negative illness perception play a key role. The cancer risk perception, as the patient's subjective interpretation of risk, represents a predictor of risk-reduction practices, processing of cancer information and lifestyle behaviours to health promotion [30, 31]. The risk perception is considered an important '*motivational engine*' for the choice of cancer risk management strategies [32]. It is a multidimensional concept for several aspects associated and it captures various meanings that an individual assigns to the experience of being at increased risk for hereditary cancer syndrome [33]. The associated factors that impact on cancer risk perception are: disease severity and prognosis, previous experience of affected relatives, coping style, self-efficacy and cancer worries. Several studies show that moderately high levels of BC risk perception constitute a predictive factor of compliance with mammography screening [34], while other variables (e.g. cancer worry, emotional distress, demographic and personality differences) moderate or mediate the association between risk perception and compliance with BC screening. An accurate perception of risk is considered an important motivational factor for health behaviours and prevention in at risk subjects, although the researchers suggest that the accurate perception of risk are hard to achieve [30]. Indeed, subjects at risk often overestimate or underestimate their cancer risk with significant impact on risk-reducing behaviours. The studies also suggest that the risk perception in at risk subjects is often associated with psychological distress and cancer worry that influence the choices of preventive measures such as surveillance, prophylactic surgery and life changes [35]. In addition, moderate levels of cancer worry are positively associated with adherence to programs of cancer risk management, while high levels are positively associated with avoidance or excessive attention for BSE because of cancer fear. The cancer risk overestimators have commonly higher levels of psychological distress than accurate estimators [36]. During CGC it is important to assess the cancer risk perception and distress levels to personalized patient's taking charge and to optimize decision-making process and partnership between equipe and patients.

Psychosocial aspects of surveillance

In the choice of cancer risk management strategies a relevant question is whether advantages of different management options outweighs the psychological burden. Several studies demonstrated that surveillance of at risk subjects for developing hereditary cancers resulted to be associated with increased distress level and a poorer quality of life. The psychological sequelae mainly concern the awareness of being at high risk of developing cancers, and the frequent breast and ovarian examinations. Different factors are associated with adverse psychological effects, such as a positive personal and familial cancer history, the coping style and a negative illness perception. Other studies reported normal levels of distress and a better general health in subjects that addressed surveillance compared to the general population [37].

Despite the heterogeneity of the studies, many researches are in agreement that the coping style is an important psychological variable associated with distress and quality of life. In particular, passive coping style, pessimistic personality, substance use, a little social support and an excessive concern for health seem to have a significant negative impact on the psychosocial well-being. A previous study, aimed at exploring the psychological adjustment and the compliance with BC surveillance in high-risk women, identified subgroups of vulnerable women, including young women performing excessive BSE, women overestimating their risk of developing BC and women with a sister affected with BC [38]. Some studies confirm a positive impact of the coping style on psychological distress. In particular, it seem that an active coping style focused on research into social relationships, expressing emotions, and an attitude of confidence and hope were significantly associated with lower levels of psychological distress. On the contrary, women using passive and palliative coping style experienced increased levels of distress [39, 40]. In order to offer tailor-made CGC, the clinicians should pay attention to identify more vulnerable women that may have high levels of psychological distress and that need psychological treatment [39].

Numerous questions remain unanswered regarding the optimal cancer risk management in BRCA1/2 carriers. Moreover, a careful evaluation of the positive and negative effects of the available options is needed. Data on the psychosocial implications of various risk management choices are critical for informed decision-making process in both patients and multidisciplinary equipe. It is necessary that during CGC process the subject at risk takes an active role, facilitated by a personalized approach and a focus on the patient's emotional state. The decision-making process needs of comprehensible information on medical, genetic and psychosocial factors. An integrated multidisciplinary approach in CGC is required to support women with high inherited risk of developing hereditary cancers in the complex decisions related to cancer risk management choice [41].

Psychological sequelae of prophylactic surgery

Several studies have evaluated the psychological variables associated with the risk management strategies as well as the psychosocial impact of the choice. A recent study, in agreement with previous results, showed that prophylactic surgery is an option widely chosen by hereditary BC patients (62%) [42]. Even among healthy women a substantial number (30%) choose prophy-

lactic measure, mainly before 44 years of age (75%). The prophylactic surgery involves risks and benefits. Potential benefits concern a reduction of BC risk and it allows a psychological peace of mind. Potential disadvantages include the invasiveness of the procedure, and the consequent morbidities. Some studies reported a positive association among choice of the BPM, increase of anxiety levels and feelings about the inevitability of cancer. The main motivation for choosing BPM is to significantly reduce the risk of developing a BC [18]. Studies results showed that women who undergo prophylactic surgery reported high satisfaction, low regret and few adverse psychosocial sequelae at a mean follow-up of 10 years after prophylactic surgery [43]. Other studies did not show any significant differences in terms of general well-being for both women who chose a risk-reducing strategy and those who did not. Most of the studies have found that women reported satisfaction with their decision, while only a small proportion of women reported dissatisfaction or regretted their decision to have a BPM. In addition, data on emotional concern in this setting reported a diminished level of emotional adverse sequelae about developing BC in 74% of those having prophylactic surgery.

The choice of preventive strategies for BRCA1/2-related cancer risk management of BRCA carriers depends on many factors, such as information process, cancer worry, anxiety and depression levels, cancer risk perception, family history and having young children. Some studies report that BPM can reduce psychological distress morbidity related to cancer risk perception, but may have a negative impact on sexuality and body image. Data about sexuality ranged from no one reporting change in sexual well-being activity or pleasure following BPM to 23% [18] reported adverse effects in feelings of femininity and 12% negative change in body image [44]. In particular, study results highlight the need to know the impact of preventive strategies on the psychological condition in order to better manage decision-making processes with BRCA1/2 carriers.

It is important to choose a management option strategy consistent with one's risk profile and emotional condition. Studies suggest the need of a personalized approach for at risk women tailored on their specific needs, including also information on medical and psychological sequelae. Beyond the informational needs, there is an emotional dimension to BPM. During decision-making process, it may be important to underline that women can take their time in assimilating information and talking it with others [34]. In addition, it is also recommended to have the availability of psychological counseling and emotional support during decision-making and postoperative adjustment periods.

The recent Angelina Jolie's announcement about BPM led other at risk women to consider similar risk management options. Psychiatrists and psychologists have emphasized the importance to encourage patients to talk openly about several issues associated with BPM (i.e. their fears, doubts, sexual intimacy) by an empathic approach. It is also important to elicit the patients to experience psychological reactions associated with BPM, knowing that such feelings are normal and will subside over time [45].

Conclusions

BRCA1/2-related BC can be considered a separate entity compared to sporadic ones. The identification of hereditary BC allows an adequate management of patients, including CGC that involves a multidisciplinary team (i.e. geneticist, oncologist and psychologist). An integrated multidisciplinary approach in CGC is required to support women with high inherited risk of developing hereditary cancers in the complex decisions related to cancer risk management choice. Risk management includes surveillance for at risk body sites, prophylactic surgery and chemoprevention. A topic in evolution concerns specific chemotherapy for BRCA1/2 carriers. A patient-centered approach is needed for at risk women tailored on one's psychosocial characteristics.

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