From adjuvant to preventive breast cancer treatment: bridging the gap over troubled waters

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Recently, chemoprevention trials have demonstrated the efficacy of preventive medical treatment (PMT) in reducing breast cancer (BC) detection rates in at-risk affected and unaffected women selected according to clinical and/or familial risk criteria, particularly with the use of tamoxifen (TAM). Major concerns limiting the routine use of TAM are the questionable benefit/risk ratio and poor patient compliance, which justify the studies undertaken to determine the efficacy of aromatase inhibitors (AIs) with respect to TAM. Issues such as therapy duration, impact on survival, incidence of side-effects and which subsets benefit most from treatment, still remain unsolved. Therefore, only ER+ BC patients are routinely subjected to PMT, independently of their BRCA1/2 status, using adjuvant hormonal therapy. More attention must be focused towards BRCA1/2 carriers as they are probably the women at highest risk of developing BC, in which available data remain controversial and in which hormone-therapy might be important. Hence, at-risk women (affected patients or unaffected women) should be carefully evaluated for inclusion into highly selected preventive clinical trials aimed at evaluating PMT independently of, or according to, BC predisposition status (unknown, positive or negative BRCA1/BRCA2 status) and with respect to menopausal status. BC patients, harboring a BRCA1/2 predisposition, may represent the best subset for extended adjuvant treatment, useful as PMT, simultaneously. Only the evolving differentiation of categories of at-risk women will allow physicians to discriminate PMT in a highly selective manner.

Key words: Breast cancer, at-risk women, prevention, aromatase inhibitors, tamoxifen

Prevention strategies in at-risk women

Today, evidence-based data strongly suggest that BC can be prevented in healthy women by anti-estrogenic approaches. The role of estrogen in the proliferation of breast cancer cells is well documented. A high estrogen level is associated with an increased risk of breast cancer, and local estrogen synthesis through aromatase activity may also play an important role in the development of BC. In fact, in the last few years, chemoprevention trials have demonstrated the overall efficacy of preventive treatments in reducing ER+ BC detection rate (31%–90%) in at-risk women selected according to clinical and/or familial risk criteria. In particular, estrogen withdrawal by use of tamoxifen (TAM) [1–3, 5] or oophorectomy [4] has shown to approximately halve invasive BC development in affected or unaffected individuals, independently of their BRCA1/2 status. BC risk reduction is particularly evident in postmenopausal women and in those showing a positive BC family history.

In fact, in the NSABP-P1 chemoprevention trial (in which women were selected according to Gail criteria), retrospective BRCA1/2 genotyping performed only in the 320 women who developed BC shows that TAM-induced BC risk reduction is evident in the 301 at-risk women not harboring a BRCA mutation whereas in the 19 (5.9%) BRCA+ women, BC risk reduction is evident in BRCA2, but not in BRCA1, carriers [5]. Moreover, BCs developed in BRCA1 carriers were mostly ER negative (6/7, 86%) while those developed in BRCA2 carriers were prevalently ER+ (6/9, 67%). Thus, it could be that TAM may be more effective in BRCA2 carriers than in BRCA1 carriers due to ER expression.

However, if oophorectomy, performed before the age of 35 in cancer-free women, is effective in reducing BC incidence among BRCA1/2 positive women [6–11] and adjuvant TAM therapy reduces the incidence of contralateral BC in BRCA1/2 positive patients [12, 13], then it is probable that hormone-therapy might have a role to play early in the course of BC development, even in BRCA1 positive tumors [14].

Ultimately, one of the major challenges in the field of BC prevention is to learn to recognize the subset of patients and "non-patients" truly at-risk of developing BC (defined by clinical
and/or familial risk and/or BRCA1/2 genetic predisposition status) on which to focus the spotlight of PMT. In particular, more attention must be focused towards women carrying BRCA1/2 mutations as they probably represent the small subset of women at highest risk of developing BC and in which PMT data will represent the basis to better comprehend the larger set of at-risk women: those in whom no known genetic predisposition is detectable.

At present, the preventive options that are conventionally proposed to unaffected BRCA1/2 carriers are: diagnostic surveillance, bilateral prophylactic mastectomy (bPM) and bilateral prophylactic oophorectomy (bPO). These preventive options represent different alternatives, from one extreme to another, to an unsolved problem [15].

1 Diagnostic surveillance aims at improving BC cure rate as diagnosis should be as early as possible. However, major limitations to this approach exist [16, 17] and are represented by the need to wait for BC development and detection, the sensitivity of available diagnostic techniques (capable of identifying only macroscopic BC lesions and not those of a few millimeters) and the possibility of performing biopsies of suspicious lesions with respect to their volume and position. Moreover, a more stringent surveillance programme does not translate into a survival advantage.

2 Prophylactic surgery consistently reduces BC incidence: bPM reduces BC incidence by 95% or 90% whether or not associated with bPO, respectively [9, 18]; bPO alone reduces BC incidence by approximately 50% [6, 10]. Both bPM and pBO are irreversible procedures, even if bPO represents the most frequently accepted option by ‘non-patients’ when childbearing is over.

Nonetheless, each of the above-mentioned alternatives is associated with variable degrees of psychological distress [19, 20] and should therefore be correlated to, and tailored on, the specific BC risk of each individual.

While prophylactic mastectomy and oophorectomy are effective in reducing breast cancer risk, they carry substantial drawbacks, including loss of body integrity in the former and systemic effects of premature menopause in the latter.

**Preventive medical treatment: where we’re at**

With respect to the available preventive measures, PMT lies in the midst of two extremes and may represent an attractive alternative for unaffected, at-risk women, especially BRCA1/2 carriers.

Although TAM definitely reduces BC incidence and osteoporosis, the IBIS-I [2] and NSABP-P1 [21] trials indicate that thromboembolic events and increased relative risk of endometrial cancer (RR 2.5) are the most worrisome pitfalls of TAM, limiting its routine use in the preventive setting [22]. In fact, the frequency with which it is proposed to, and accepted by, healthy at-risk individuals is actually quite low: recent studies show that among healthy at-risk individuals (even BRCA positive women) less than 50% are informed about TAM prophylaxis by their physicians, a maximum of 18% accept prophylactic TAM and over 82% refuse it because of its potential adverse effects [23–25]. Today, efforts are being made to reduce these adverse effects: completed adjuvant and ongoing preventive clinical trials will define the efficacy, the side-effects and the better or worse tolerability of specific AIs (anastrozole, exemestane, letrozole) with respect to TAM or raloxifen. For these reasons, the medical world is tackling the dilemmas of which drugs suit PMT best, their impact on mortality, the incidence of co-morbidities, which women benefit most from PMT and optimal PMT duration.

An adjuvant or prevention BC trial represents an endeavor of many years with substantial difficulties, particularly those concerning accrual, the major bottleneck in scientific progress [26, 27]. However, a trial aimed at a highly selected at-risk population (ex. BRCA positive post-menopausal women) would require a lower accrual and number of events to demonstrate its benefit or ineffectiveness. By contrast, such a study would require much more time (quite a few months) for women to be enrolled, considering the time necessary for BRCA1/2 testing of a suspected BC patient to be carried out, followed by that of BRCA1/2 segregation analysis in healthy family members, representing potential recruitment subjects.

Despite all the above, the BC PMT setting is only apparently surrounded by a mist of unresolved and confusing issues: a closer look indicates that, in reality, progress has been made and certain ‘cornerstones’ have been laid within the PMT setting.

**Preventive medical treatment: past, present and future drugs**

Ever since BC occurrence has been known to be associated with estrogen exposure, the estrogen receptor is the molecular target against which BC treatment and prevention have been aimed. Today, the estrogen receptor can be ‘silenced’ either by binding it to substances that block its function or by abrogating estrogen production.

Much attention has been dedicated to understanding how and when to use anti-estrogen therapy, especially TAM, for the treatment of BC in the metastatic and adjuvant settings, and anti-estrogen therapy is now, theoretically, accepted as a preventive BC measure in healthy, at-risk women. The term ‘at-risk woman’, however, still remains an equivocal definition encompassing various well-established factors known to influence BC risk: clinical criteria (nulliparity, early menarche, advanced age), positive family history and genetic predisposition (BRCA1/2 status).

Unfortunately, TAM’s adverse effects have limited its proposal and use in the preventive setting, explaining the growing number of chemoprevention studies undertaken to replace TAM with newer, less risky agents, such as AIs and second generation SERMs.

Results from breast cancer prevention trials leave several unanswered questions regarding optimal preventive therapy, including how durable the preventive effect is and who benefits the most. In addition, it is unclear how preventive therapy interacts with HRT and whether hormonal therapy is effective in BRCA1/2 carriers. In fact, considering that BRCA1 is implicated...
in processes of DNA repair and gene expression, and that it is intimately related in the BASC complex with Mlh-1, Msh-2, ATM, Bard, Nibrin and Rad 51, it is not possible to exclude the fact that SERMs may also stimulate BRCA-mutated cell growth. Recently, third generation AIs have emerged as equivalent or superior drugs, when compared with TAM, both in the metastatic and adjuvant BC treatment settings [28–33]. Moreover, contrary to TAM, AIs do not seem to increase thromboembolic events and relative risk of endometrial cancer [34]. At worst, AIs could negatively affect bone metabolism since they deprive the body of estrogens. In fact, in the anastrozole arm of the ATAC trial, fracture rate was significantly higher than that of the TAM arm.

Exemestane, a particular AI, seems to be promising in the BC prevention setting [35, 36]. In fact, preclinical studies show that exemestane abrogates estrogen production by 98%, induces a progressive reduction of aromatase levels and has a better safety profile, with respect to other AIs, since it does not affect lipid and bone metabolisms negatively [37, 38].

However, it must not be forgotten that a BC cell can probably be tackled in more than one way. In fact, AIs seem to have superior antitumor activity in the subgroup of ER+/PR- BCs, especially in those expressing the Her2 receptor [39, 40]. Tamoxifen may be less effective in tumors that are both ER and HER2 positive, because HER2 and ER intracellular signaling pathways are interlinked and HER2 signaling in BC may stimulate estrogenic effects of tamoxifen.

Although only 6% of BRCA1/2 carriers develop BCs with HER2 overexpression, in this specific subset of women [41], monoclonal antibody PMT (trastuzumab) may also be a potential prevention tool to be used alone, or in combination with anti-estrogen PMT. However, further studies concentrating on the molecular characterization of both BCs and benign proliferative breast diseases, developing in BRCA1/2 carriers and non-carriers, are warranted to define new molecular targets for innovative and individualized preventive therapies.

**breast cancer adjuvant treatment: issues for improving preventive medical therapy**

As far as PMT duration is concerned, past and present investigations seem to unanimously report that, in the adjuvant setting, TAM should be used for at least 5 years [42]. Since BC patients have a protracted risk (20% at 10 years) of local, contralateral or distant disease after 5 years of TAM therapy [43–45], several trials have been designed to investigate 5-year TAM treatment versus extended 10-year anti-estrogen treatment using TAM alone, or for 5 years followed by 5 years of an AI.

Whereas the use of TAM alone for 10 years does not seem beneficial [1], extended anti-estrogen treatment using an AI, after 5 years of TAM, not only reduces BC events but also benefits absolute disease-free survival by about 2% [32, 46]. This reduction is evident in ER+/PR+ BC patients but is greater for ER+/PR– patients [47].

However, if the residual relapse rate of BC patients, after the first 5 years, is 4% each year thereafter (up to 10 years) and extended combination of anti-estrogen treatment reduces BC events by, on average, 1.5% per year [46], then no more than one-third of BC patients benefits from extended adjuvant treatment.

These results represent a milestone, which should be used as a starting point, from which to address and identify who are the few women that truly benefit from PMT (N+, subsets of ER+ BC) since it is difficult to recommend extended adjuvant treatment in BC patients when approximately 2% of BC patients/year benefit.

**preventive medical treatment: where we’re going**

Considering that BRCA1 and BRCA2 are involved in approximately 85% of BC predisposition (45% for BRCA1; 40% for BRCA2), that the cumulative risk of BC development ranges between 56% and 80% [48] and that estrogen positivity is seen in 66% and 10% of BRCA2 and BRCA1 carriers, respectively [41], it can be assumed that overall, 30%–40% of BCs developing in BRCA carriers will be ER+ and consequently suitable for PMT through estrogen blockade. In this context, BRCA2 mutation carriers may be the subset that benefits the most from anti-estrogen PMT while chemoprevention by estrogen blockade of the development of ER- BCs, prevalent in BRCA1 carriers, is yet to be elucidated.

If it is true that physicians, patients and healthy at-risk women must take part in chemoprevention trials without reluctance, it is also true that physicians and women must have a selection of well-designed and well-targeted chemoprevention trials to facilitate their decision.

Ongoing chemoprevention trials, such as IBIS-II (comparing placebo versus anastrazole) and STAR (TAM versus raloxifene), enroll women according to BC family history and/or clinical criteria without considering BRCA status. And yet, according to the previously mentioned lifetime BC risk in BRCA1/2 carriers (56%–80%), BRCA1/2 carriers show a relative risk six to eight times greater compared to a 10% cumulative BC lifetime-risk of women in the normal population. In particular, BC risk due to BRCA1 or BRCA2 mutations seems to be 20% by the age of 40, 55% by age 60 and over 80% by age 80 [49]. Moreover, effective BC detection rate in this particular category is about 3% per year [50]. Thus, BRCA1/2 status is always more important and should always be considered, when possible, for the PMT setting. In postmenopausal BRCA1/2 carriers, the ongoing Aromasin Prevention Study (A.Pre.S.) study (comparing placebo versus exemestane) will answer the question of whether chemoprevention, using an AI, is effective in preventing BC in this particular set of women.

In BRCA positive families, representing approximately 20%–30% of those at-risk families selected according to criteria justifying genetic testing (>10%), BRCA1/2 carriers (postmenopausal ‘non-patients’ and previously affected BC patients) should be recruited in prevention trials selecting women according to their predisposition status.

At-risk BRCA1/2 negative families (70%–80% of those at risk) and untreated at-risk families (at risk according to other risk criteria), should be recruited in prevention trials according to BC family history and/or clinical criteria.
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In healthy, at-risk women (independently of a positive, negative or unknown genetic predisposition status) preventive hormone therapy can be proposed only within controlled clinical trials.

In genetically predisposed women, previously affected by hormone-sensitive BC (ER+), adjuvant hormone therapy (5–10 years) is also effective in reducing the development of secondary BCs.

Among at-risk women, previously affected BC patients (more than 5 years), also at risk of new BCs due to BRCA1/2 predisposition, may represent another subset of women suitable for both extended adjuvant treatment and PMT at the same time. Once again, this justifies the pursuit in identifying those women who truly benefit from extended adjuvant treatment, as well as from PMT, since in the future anti-estrogene adjutative or preventive treatments should be restricted and tailor-made to fit only these women (Table 1).

To date, despite the growing evidence in favor of anti-estrogen PMT, only at-risk women previously affected by ER+ BC (particularly more than 5 years before) are proposed to receive an anti-estrogenic 'preventive' therapy (aimed at controlling local, contratalar and distant disease) independent from their genetic susceptibility to BC (unknown, positive or negative BRCA1/2 status).

Physicians are urged to carefully select unaffected, at-risk women with unknown, positive or negative BRCA1/2 carrier status and to highly recommend these women to take part in targeted preventive clinical trials aimed at evaluating PMT independent of, or according to, predisposition carrier status and with respect to menopausal status. The evolving differentiation of at-risk women (defined by different systems such as the Gail and/or prior probability of cancer predisposition models) according to their clinical status (affected or unaffected women) and their genetic susceptibility to BC (unknown, positive or negative BRCA1/BRC2 status) will determine the orientation of PMT.

**references**


