Acceptability of chemoprevention trials in high-risk subjects

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The development and current widespread acceptance of clinical trials is one of the major conceptual advances in research medicine introduced during the second half of the 20th century. Despite general agreement on the scientific merits of randomization, many patients and physicians are however reluctant to participate in randomized, controlled trials. If we focus on chemoprevention in healthy subjects, it is even more essential to evaluate the ethics, logistics, patient’s and doctor’s acceptability, acute and late toxic effect, patient accrual and compliance of treatment. Furthermore, the decision-making process about participating in a cancer chemoprevention trial is often poorly understood. Adherence to a cancer prevention trial requires in fact a strong sense of awareness and an ability to carefully assess risks and benefits. We review the main aspects in the chemo-preventive approach to patients at high risk for breast and ovarian cancer, focusing on different pharmacological risk reduction strategies, ongoing phase III chemoprevention studies in carriers of BRCA1/2 germline mutation, the psychological and clinical factors implicated in decision making about a trial, and the possible impact of the trial design on the overall acceptability and adherence.

Key words: BRCA mutations, clinical trials, chemoprevention, ethics, patient adherence

introduction

Chemoprevention has the potential of significantly reducing the incidence of cancer [1]. Randomized clinical trials are the gold standard to assess both the efficacy and the risk-benefit ratio of such intervention but large numbers of person-years are required to reach a statistical power.

A subject who adheres to a cancer prevention trial is supposed to possess a strong sense of awareness and an ability to carefully assess risks and benefits. The decision also represents an active approach of the individual to control her/his own life in order to achieve a state of well-being and an enhanced quality of life [2]. On average, regardless of the kind of survey, acceptability of chemoprevention trials is not high, ranging from 22.1% to 34.0% for breast cancer prevention [3, 4]. The present article reviews the most important aspects in the chemo-preventive approach to patients at high risk of developing breast and ovarian cancer, different drug options, some ongoing phase III studies, the psychological and clinical factors implicated in decision making and the possible impact of the study design in the acceptability and acceptance to participate in a trial.

selective estrogen receptor modulators and aromatase inhibitors

Tamoxifen is a selective estrogen receptor modulator (SERM) that has an inhibitory effect on estrogen receptors (ERs). The preventive effect of tamoxifen in patients with a hereditary predisposition has been extrapolated mainly from studies analyzing the incidence of contralateral breast cancer in BRCA1/2 mutation carriers who were treated with tamoxifen after their primary breast cancer diagnosis.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) started in the 1980s the breast cancer prevention trial (P-1) on 13 388 high-risk patients to evaluate the efficacy of tamoxifen in reducing breast cancer risk [5]. In the subset of healthy individuals with a BRCA2 mutation receiving tamoxifen, the risk of breast cancer was reduced by 62% relative to placebo [risk ratio = 0.38; 95% confidence interval (CI) 0.66–1.56], similar to the reduction of ER-positive breast cancer among all women in the same breast cancer prevention trial. In contrast, tamoxifen use did not significantly reduce breast cancer incidence among women with inherited BRCA1 mutations. However, the results of the study were limited by the small number of patients in this high-risk cohort. According to other studies, it has been estimated that tamoxifen reduces breast cancer risk in BRCA1 mutation carriers by 13% and in BRCA2 mutation carriers by 27%, and similar results were found with respect to the reduction of contralateral breast cancer risk in patients with a BRCA1/2 mutation treated with tamoxifen after first diagnosis of breast cancer [6–9].

A case–control study looking at BRCA1/2 mutation carriers who developed bilateral breast cancer (n = 285) versus those who had unilateral breast cancer (n = 781) showed a protective effect of tamoxifen among women who were premenopausal or who had undergone natural menopause (OR = 0.44; 95% CI 0.27–0.65) suggesting that the use of tamoxifen in BRCA1/2 mutation carriers who have not undergone a bilateral...
salpingo-oophorectomy (BSO) may result in a decreased risk of breast cancer [9]. In another case–control study of women with either BRCA1 or BRCA2 who developed contralateral breast cancer, tamoxifen was associated with a decreased incidence of contralateral breast cancer (OR: 0.50; 95% CI 0.28–2.09) (OR: 0.38; 95% CI 0.19–10.74 and OR: 0.63; 95% CI 0.20–21.50, for BRCA1 and for BRCA2 mutation carriers, respectively) [8].

Two additional major chemoprevention trials, the Study of Tamoxifen and Raloxifene (STAR trial) and the study of Exemestane for primary prevention of breast cancer in postmenopausal women (NCIC CTG MAP.3 trial) unfortunately did not address the effects of raloxifene and exemestane, respectively, in women with BRCA mutations. Another small Italian randomized study of exemestane in postmenopausal BRCA1/2 mutation carriers (ApreS trial) was stopped prematurely a few years ago due to very poor accrual. Currently ongoing is a randomized clinical trial by the French Federation of Cancer Centers investigating the preventive effect of the aromatase inhibitor letrozole in postmenopausal women with BRCA1/2 mutations (ClinicalTrials: NCT00673335). Preliminary data on accrual into the trial show an overall 15% of acceptability among all eligible subjects; women with previous unilateral breast cancer or prior prophylactic oophorectomy were most likely to enter such prevention trial [10].

oral contraceptive pill

It has recently been accepted that oral contraceptive pill (OCP) use decreases the risk of ovarian cancer in the general female population. However, much debate has ensued on whether the OCP increases some women’s risks of developing breast cancer [11–13]. A recent meta-analysis [14] on the association between OCP use and breast or ovarian cancer in BRCA1/2-mutation carriers showed that OCP use at any point during their lives was associated with a 50% relative-risk reduction in developing ovarian cancer. Looking specifically at duration of OCP use, each 10-year period of OCP use resulted in a 36% relative-risk reduction for the development of ovarian cancer. No evidence of a significant association between OCP use and breast cancer risk [summary relative risk (SRR): 1.13; 95% CI 0.88–1.45] was observed. Specifically, very old OCP formulations in use before 1975 correlated with an increased risk of breast cancer (SRR: 1.47; 95% CI: 1.06–2.04), but no such correlation was found with the use of more recent, post-1975, formulations (SRR: 1.17; 95% CI 0.74–1.86).

targeted therapies for BRCA-deficient tumors

BRCA1 plays an important role in maintaining genomic integrity by protecting cells from double-strand breaks (DSB) that arise during DNA replication or after DNA damage. In turn, BRCA1-deficient tumor cells are more vulnerable to DNA damaging agents such as platinum-based chemotherapy. Poly (ADP-ribose)polymerase inhibitors (PARPi) are novel treatment options for ovarian and breast cancers targeting preferentially BRCA1-deficient cells and likely sparing those with normal homologous recombination [15]. PARP enzymes are implicated in the repair of single-stranded DNA breaks (SSBs) and unrepared SSBs lead to DSBs, which are subsequently repaired in cells with normal BRCA function. In BRCA-deficient or nonfunctioning cells, DSBs are left unrepaird with consequent genomic instability and cell death [15]. Among PARPi, olaparib has been studied in phase I and II clinical trials for the treatment of advanced breast and ovarian cancer patients with BRCA1/2 germline mutation with promising results [16, 17]. A number of clinical trials are currently ongoing with the use of various PARPi, either as single agents or in combination with chemotherapy, for both hereditary and sporadic breast and ovarian cancer. However, the insufficient knowledge of the actual effects of PARPi on unaffected breast tissue of germline mutation carriers, added to the potential for side-effects, suggest caution at present in considering the possibility of any chemoprevention trials with PARPi in healthy subjects.

the synthetic retinoic acid derivative fenretinide

Retinoids are a class of compounds chemically related to vitamin A that are able to activate and/or repress specific genes and consequently suppress tumor promotion and/or modify some properties of cancer cells [18]. Retinamides are synthetic retinoids modified in order to enhance target organ specificity, increase anticarcinogenic activity, and reduce toxic effect [19].

Fenretinide or N-(4-hydroxyphenyl)retinamide (4-HPR) is the synthetic amide of retinoic acid which has shown preferential accumulation in the breast tissue [20], as well as higher activity and lower toxic effect compared with other retinoids [21]. In animal models, fenretinide was shown to suppress the recurrence of mammary cancer after primary tumor removal [22] and to inhibit the progression of ductal hyperplastic lesions and ductal carcinoma in situ [23]. Its mechanism of action is incompletely known but its inhibitory effects are believed to be related to both receptor dependent and independent mechanisms [24–26]. The binding of retinoids to the nuclear receptors leads to the regulation of several cellular processes, including growth, differentiation and apoptosis [27]. However, fenretinide is also able to inhibit the proliferation of breast cancer cells that do not express retinoic acid receptors (RARs) [24]. A unique feature of fenretinide is the ability to inhibit cell growth proliferation through the induction of apoptosis rather than differentiation—an effect that differs totally from that of all-trans retinoic acid [28, 29].

The over 15-year follow-up of a randomized phase III trial [30] of fenretinide to prevent second breast cancer has indicated an overall 17%, durable reduction of second breast cancer incidence induced by fenretinide. More importantly, when stratified by menopausal status, the analysis showed a 38%, statistically significant reduction of second breast cancers in postmenopausal women and this protective effect persisted for up to 15 years, i.e. 10 years after treatment cessation. Notably, the younger the women, the greater was the trend for a benefit from fenretinide, with a remarkable 50% risk reduction in women aged 40 years or younger, whereas the benefit disappeared after age 55. One explanation for the different
effects of fenretinide according to menopausal status or age is a different modulation of circulating IGF-I in premenopausal and postmenopausal women, with a reduction of IGF-I levels only occurring in premenopausal subjects.

Additional fenretinide mechanisms have been investigated, such as the capability of retinoids to inhibit cell growth by reducing the expression of growth-stimulating factors or by inducing the expression of growth-inhibitory factors. In vitro, fenretinide is correlated both with a decreased secretion of insulin-like growth factor-I (IGF-I), a stimulator of epithelial cell growth, and an increased secretion of IGF-binding proteins (IGFBPs) [31, 32]. Higher circulating insulin-like growth factor-I levels are associated with greater risk of developing subsequent breast cancer in premenopausal women [33] and fenretinide has shown to be able to decrease plasma IGF-I levels [34, 35]. Noteworthy during this intervention there were six cases of ovarian cancer in the control arm vs. none in the treated arm; at 15 years of follow-up, however, 10 cases in the control group and 6 in the fenretinide group have been observed. These latter results are not statistically significant and the effect on ovaries requires further study.

Fenretinide is also highly effective in inhibiting the growth of BRCA-1 mutated breast cancer cell lines [36]. Finally, recent studies have shown that 4-HPR modulates gene expression in ovarian cells, with an upregulation of expression of proapoptotic genes in OVCA433 cells and downregulation of mutant BRCA genes in IOSE (premalignant) cells and OVCA433 cells [37].

The prolonged, carry-over effect demonstrated in the first phase III trial has been accompanied by a very low toxic effect profile (mainly reversible skin dryness and rashes and dark adaptation difficulties, often overcome by a monthly weekend suspension of the drug) [30]. Like other retinoids, fenretinide may be potentially teratogenic, although available studies show no genotoxic effects in vitro and limited effects in vivo and a lack of storage in the human embryo. Nevertheless, appropriate measures of contraception must be adopted when treating potentially fertile women.

As a reduction of second breast cancer might be a surrogate marker of primary prevention, such a favorable effect of fenretinide in premenopausal women provides a strong rationale for a primary prevention trial in unaffected women at high risk of breast cancer [38]. If we consider its protective activity on second breast cancer in young women and a similar trend on ovarian cancer, at least during intervention, it appears that women with germline BRCA 1 and 2 mutations may be ideal candidates for further investigation of this retinoid. Accordingly, the European Institute of Oncology (Milan, Italy) has activated a multicentric randomized phase III placebo-controlled prevention trial addressed to this particular cohort of women. This project is a study. A total of 764 healthy women at increased breast cancer risk will have to be randomized to 4-HPR 200 mg/day versus placebo for 5 years. The subjects will be stratified by participating center and breast cancer risk (BRCA1 versus BRCA2 mutation versus high-risk subjects). The primary end point is the incidence of invasive breast cancer and ductal intraepithelial neoplasia. Secondary end points are the incidence of other noninvasive breast disorders (i.e. intraepithelial lobular neoplasia and atypical hyperplasia), ovarian cancer and other cancers. Moreover, we planned to further investigate the mechanisms of action of fenretinide in preventing breast cancer. Early and intermediate biomarkers of efficacy after 12, 36 and 60 months of treatment, genetic interactions with breast cancer risk modifiers will be explored with the primary goal to identify molecular biomarkers of response prediction. In particular, we will evaluate the percentage change in circulating biomarkers of the IGF system, androgens, retinol binding protein (RBP4), insulin and blood glucose after 12, 36 and 60 months of treatment. In a subgroup of participants, fine needle aspirate breast biopsy or cells obtained from breast ductal lavage will be drawn at baseline and after a 12-month treatment and the percentage change in RAR expression correlated with apoptosis (caspase-3) and proliferation (Ki67). The results will be correlated with mammographic density, and plasma and tissue biomarkers after 1-year treatment. Fenretinide and its metabolites will also be measured to investigate drug bioavailability and compliance. Should the results of this trial confirm that fenretinide is effective in reducing breast and ovarian cancer incidence in this very high-risk population, that this effect lasts for many years after treatment, and that the tolerability profile is very good, we will have a further powerful preventive agent and a new risk reduction option.

acceptability and future directions

Recently, Pujol et al. examined the feasibility and the uptake of the LIBER trial, a randomized breast cancer prevention trial comparing letrozole to placebo in postmenopausal women with BRCA1/2 mutations [10]. The acceptability was 32%. However, since only 44% of women invited by mail underwent a consultation, the overall enrollment rate in eligible patients decreases to 15%. The IBIS1 and IBIS2 trials showed an uptake rate of 8.4% and 12% in very high-risk and high-risk populations, respectively [39]. Thus, the results of the LIBER trial are in line with the acceptability of other prevention trials and even higher than the uptake of tamoxifen in BRCA1/2 mutation carriers [40–43]. Notably, a higher percentage of women who entered the LIBER study had a first cancer, suggesting a stronger motivation for chemoprevention in the subgroup of previously affected subjects.

Overall, the relatively low acceptability rate of cancer chemoprevention trials clash when compared with the uptake of highly accepted studies on chemoprevention of cardiovascular diseases [44, 45]. The widespread diffusion of cancer preventive strategy will require time but, if we consider that, during the 1960s, the acceptability of the chemo-preventive approach to cardiovascular disease was half than today [45], it is likely that, in the next future, a correct communication, information and education to a healthy lifestyle will lead to a similar shift towards a much higher acceptability of cancer prevention. Moreover, the acceptability of a cancer chemoprevention study may be related to different patterns of the decision-making process. The presence of a randomization has been often reported as a possible cause of refusal of a clinical trial [43] but data are controversial [46] and probably due to differences in cultures, attitudes and behaviors of people around the world [47, 48]. Furthermore, the duration of the proposed trial is another important issue: again in the LIBER trial people agreed
on short-term trials of 1 year or less and disagreed on longer trials [46], and these data are coherent with the observed dropout rates in other preventive trials [49].

Various research and clinical assistance modalities may strongly help to increase acceptability of medical prevention in the form of clinical trials. Multidisciplinary approach of dedicated staff in appropriate facilities is needed, together with easy access to regular communication, decision counseling and psychologic support. We have to promote more studies not only on drugs, but also on natural compounds/vitamins/micronutrients and more phase II studies on surrogate biomarkers before embarking on large scale phase III studies on cancer incidence and mortality: as said before, shorter study periods are better accepted, both for entry and retention during follow-up.

In conclusion, it is now clear and largely accepted that a sound personalized approach by experienced personnel in cancer prevention, taking care of tailoring that individual’s own route which may include intensive surveillance, lifestyle modifications, chemoprevention and prophylactic surgery as options, not only in complementary but also sequential fashion during lifespan, is the most effective strategy. All this should be modulated case by case and may be changed with appropriate flexibility during time according to rising research data and the subject’s characteristics and preferences.

disclosure

The authors have declared no conflict of interest.

references


