Preoperative Systemic Treatment in BRCA-Positive Breast Cancer Patients: Case Report and Review of the Literature

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Keywords

Preoperative chemotherapy · BRCA mutation · Breast cancer

Summary

Background: In vitro and in vivo analyses have shown differences in chemosensitivity between breast cancers associated with BRCA1/2 mutations compared to sporadic variants. In the preoperative setting, the tumor response can be directly measured. Therefore, preoperative systemic treatment (PST) offers the opportunity to assess the chemosensitivity in vivo. However, there have been neither clear guidelines for mutation carriers in terms of choice of chemotherapy regimen nor recommendations how to proceed in case of an inadequate response to PST. **Case Report:** Herein, we present the history of a 39-year-old woman with bilateral breast cancer who was tested positive for germ-line BRCA1 mutation while under PST. We performed a comprehensive literature review covering the MEDLINE database from 1992 to 2010 on published data regarding PST options for BRCA mutation carriers. **Conclusions:** If results of genetic testing are obtained during PST, individual therapy adaptations can be discussed with respect to mainly retrospective data of response to specific drugs. However, larger studies with longer follow-up are eagerly needed to draw firm conclusions before any specific treatment recommendations can be given for BRCA mutation carriers. PST is an ideal setting to evaluate such treatment options and to describe predictive markers that can help define subgroups that benefit most.

Schlüsselwörter

Präoperative Chemotherapie · BRCA-Mutation · Mammakarzinom

Zusammenfassung

Hintergrund: In-vitro- und In-vivo-Untersuchungen haben gezeigt, dass es Unterschiede in der Chemosensibilität zwischen BRCA1/2-bedingten und sporadischen Mammakarzinomen gibt. Im Zuge einer präoperativen systemischen Therapie (PST) kann das Ansprechen eines Tumors direkt gemessen werden, sodass Rückschlüsse auf einen individuellen Therapiebenefit gezogen werden können. Es wurde eine problemzentrierte Literaturrecherche in MEDLINE-Zitaten zwischen 1992 und 2010 durchgeführt, um die Datenlage für Chemotherapieoptionen bei BRCA-Mutationsträgerinnen darzustellen. **Fallbericht:** Wir berichten von einer 39-jährigen Patientin mit bilateralem Mammakarzinom, die während der PST positiv auf BRCA1 getestet wurde. **Schlussfolgerungen:** Wenn während der PST genetische Testresultate gewonnen werden, können individuelle Therapieanpassungen hinsichtlich meist retrospektiver Daten des Ansprechens auf spezifische Medikamente diskutiert werden. Größere Studien mit längerem Follow-up sind jedoch dringend nötig, um Therapien und Behandlungspfade für BRCA1/2-Mutationsträgerinnen empfehlen zu können. Die PST stellt optimale Studienbedingungen dar, um Therapieoptionen und prädiktive Marker zu finden und um die Subgruppen zu definieren, die am meisten profitieren.

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Introduction

Breast cancer (BC) has been recognized as a heterogeneous disease with variable tumor subtypes that differ in prognosis and response to therapy [1]. A precise tumor classification based on tumor biology and genomic imprint promises substantial advances for more targeted therapies. In 25–40% of BC patients under the age of 35 years, BC is associated with predisposing genetic variants. In approximately 50% of the hereditary origin, mutations in the BC genes, BRCA1 or BRCA2, are detected [2]. Differences in chemotherapy response between BRCA mutation carriers and non-carriers have been outlined by multiple preclinical studies as well as mainly retrospective clinical analyses [3–6]. Although more than a decade of research has enlightened our knowledge of BRCA gene function, this has not yet influenced the selection of drug treatment nor led to specific guidelines for therapy of BRCA1/2-associated BC [7]. It remains challenging to define the right therapeutic regimen for the right patient [8]. Thus far, only preoperative systemic treatment (PST) offers the possibility to directly measure tumor response in vivo at regular intervals clinically, by imaging methods and, even more important, on the microscopic or molecular level. The response rate can serve as an intermediate surrogate end point for ultimate prognosis. Currently, PST is indicated in non-metastatic primary BC to decrease the tumor bulk, thereby enhancing the possibility of breast-conserving surgery (BCS) [9]. A change in the PST regimen in case of inadequate response in non-tested patients with BC has so far not been successful [10]. In particular, BRCA test results have not yet been addressed with respect to their potential for a more individualized therapy.

We present the history of a young women tested positive for a BRCA1 mutation while undergoing PST in order to achieve BCS. We performed a comprehensive literature review covering the MEDLINE database from 1992 to 2010, in order to discuss possible algorithms and the current state of the art on PST in BRCA mutation carriers, and to outline differences in response to PST between mutation carriers and patients with sporadic BC.

Case Report

A 39-year-old premenopausal, otherwise healthy woman without any family history of malignancies presented with a bilateral invasive ductal BC along with a ductal in situ component. Initial ultrasound, mammography and magnetic resonance imaging (MRI) revealed bilateral grade 2 BC (right breast cT1c multicentric cN+, left breast cT1c cN–). In both malignant lesions, the estrogen receptor (ER) was expressed in 50% and the progesterone receptor (PgR) in 20% of the tumor cells. Her2/neu was negative; Ki67 was positive in 15% of the tumor cells. There was no family history for breast or ovarian cancer. 4 cycles of epirubicin (90 mg/m²) in combination with cyclophosphamide (600 mg/m²) were applied every 3 weeks (q3w), sequentially followed by 4 cycles of docetaxel (100 mg/m²) q3w. The chemotherapy was tolerated without major side effects. Clinical

and imaging assessment of the primary tumor was performed following every other cycle of PST. Following the completion of 8 cycles, ultrasound, mammography and MRI demonstrated a partial remission according to the Revised Evaluation Criteria in Solid Tumors (RECIST), with a reduction in tumor size on both sides on MRI (77 mm versus 23 mm on the right side and 24 mm versus 16 mm on the left side). The smaller foci in the right breast and the suspicious lymph node were no longer detectable. Testing for BRCA mutations was recommended following counseling and performed under fast-track conditions, i.e. awaiting test results within 12 weeks. The test results were obtained after the third cycle of chemotherapy and revealed a BRCA1 mutation in exon 20. A skin-sparing mastectomy on the right side and BCT or prophylactic mastectomy on the left side with bilateral axillary lymphonodectomy were discussed with the patient. An immediate reconstruction within the first operation was not recommended. The patient opted for bilateral skin-sparing mastectomy with axillary lymphonodectomy in addition to a bilateral adenectomy. A diagnostic bone marrow aspiration was also performed. On the right side, besides regressive changes, the histological exam revealed a 1-mm and 2-mm rest of invasive ductal BC with intraductal component and lymphangiosis carcinomatosa stage ypT1a multicentric ypN0(0/7) L1 G2 R0. ER and PgR were expressed in 50% and 20% of the tumor cells, respectively. Her2/neu was negative. On the left side, the specimens enclosed a regressively changed 9-mm invasive tumor rest stage ypT1b ypN0(0/13) L0 G3 without expression of ER, PgR or Her2/neu. Radiotherapy of the breast and the draining supraclavicular lymph nodes on the right side was recommended. Adjuvant endocrine treatment with an aromatase inhibitor for 5 years and zoledronic acid 4 mg every 6 months was additionally advised. A genetic consultation testing of the patient's relatives was also recommended.

Discussion

BRCA Mutation and Response to Chemotherapy

Several clinical trials comparing PST to similar adjuvant chemotherapy have shown equal efficacy regarding disease-free and overall survival [11]. However, patients who achieve a pathologic complete response (pCR) following PST have a superior outcome as compared to those with extensive residual invasive disease and would therefore be the group that benefits most from PST [12]. In retrospective analyses, patients with endocrine non-responsive, high-grade, high-proliferating tumors and BRCA1/2 function deficiency demonstrated highest pCR rates of up to approximately 40–50% [13] in addition to a higher response rate to PST in general [14, 15]. No significant difference in the response rates to PST between BRCA1- and BRCA2-associated BC have been found [14], although BRCA1 mutations are more often associated with worse prognostic factors [15]. It was hypothesized that mutation carriers are more sensitive to chemotherapy due to the loss of Bcl-2 expression and thus increased apoptosis following chemotherapy [16]. On the other hand, Hubert et al. [17] suggested a higher rate of resistance to PST in BRCA1/2-associated tumors as compared to patients with sporadic BC. BRCA1/2 plays a major role in the accurate repair of DNA double-strand breaks (DDSB) by homologues recombination following chemotherapy and radiotherapy [18]. Therefore, BRCA1/2-associated BC may be particularly sensitive to DNA-damaging agents that induce DDSB, e.g. platinum-

based compounds, and drugs inhibiting salvage repair mechanisms like the repair of DNA single-strand breaks (DSSB) by base excision repair, e.g. poly(ADP-ribose) polymerase inhibitors (PARPi).

PARPi and BRCA Mutation

PARPi are small molecules that show promise in the treatment of BRCA1/2-associated breast and ovarian cancers and tumors with dysfunctional repair by homologous recombination due to dysfunctional BRCA genes (BRCAness). PARPi mainly inhibit the repair of DSSB leading to the accumulation of DDSB. In normal cells, these breaks are repaired by an error-free homologous recombination DDSB repair pathway, key components of which are the tumor suppressor proteins BRCA1 and BRCA2. Thus, BRCA1/2 mutations can result in deficient homologous recombination DNA repair, which causes genetic aberrations promoting carcinogenesis. This tumor-specific defect can be exploited by using PARPi to induce selective tumor cytotoxicity, sparing cells with the complete repertoire of DNA repair mechanisms. To date, investigations on PARPi are in advanced clinical development [19, 20].

Platinum-Based Compounds and BRCA Mutation

Platinum-based compounds have not been found to benefit the majority of BC patients [21], but among BRCA1-associated BC patients, they appear to be more effective [22]. The underlying mechanism may involve the platinum-derived inter- and intrastrand cross-linked DNA adducts [23]. 9 out of 10 BRCA1/2 mutation carriers with primary BC achieved a pCR following PST with 4 cycles of cisplatin [5]. Combination therapies of platinum compounds with PARPi and other cytostatic drugs are further evaluated to define synergistic and additive effects. In particular, PST is an attractive setting for further evaluation of such new compounds and combinations as it allows direct measurement of the tumor response in vivo and therefore enables the rapid development of predictive molecular markers.

Taxanes, Anthracycline, Antimetabolites, Combinations Thereof and BRCA Mutation

Reduced sensitivity to taxanes and doxorubicin in BRCA mutation carriers was reported in vitro and in vivo [24]. The molecular mechanism of a spindle poison such as docetaxel supporting these clinical data was described, due to the dependence on wild-type BRCA protein expression for response to paclitaxel [5, 25]. Preclinical investigations indicated that paclitaxel resistance is caused by down-regulation of BRCA1 in MCF-7 cells [26]. Byrski et al. [5] showed an inferior response rate to PST in a subgroup of BRCA1 carriers receiving docetaxel combined with doxorubicin. On the other hand, higher sensitivity in BRCA1 mutation carriers was shown with DNA-damaging agents like anthracyclines and antimetabolites [15, 27, 28]. It was hypothesized that the

increased chemosensitivity of BRCA-associated tumors to anthracyclines is due to the missing interaction of BRCA1/2 with RAD51 in the repair of DDSB [29]. Chappuis et al. [14] performed a retrospective study of 38 BC patients receiving anthracycline-based combination chemotherapy or single paclitaxel as PST. All had undergone genetic testing for BRCA mutation. BRCA1/2 mutation carriers achieved clinical complete remission (cCR) and pCR rates of 93% and 44%, respectively, as compared to 30% and 4% among non-carriers. In contrast, in a small series of 12 BRCA1 patients, the efficacy of anthracycline-based chemotherapy was inferior in mutation carriers as opposed to non-carriers [30]. An intermediate pCR rate was found in patients treated with doxorubicin and cyclophosphamide as well as those with a triple combination of fluorouracil, doxorubicin and cyclophosphamide [31]. A low rate of pCR was found in a triple combination of cyclophosphamide, methotrexate and fluorouracil [31]. Although the response rates to chemotherapy differ between carriers and non-carriers, the toxicity profiles seem to be similar between both groups [32].

Besides the fact that all these findings are only of hypothesis-generating character, it may be discussed if our patient would have benefited even better from another regimen of PST. Given the situation of knowing the BRCA status prior to the beginning of the PST, one could discuss a PARPi-including regimen – if randomized clinical trials were available. On the other side, our review of the literature revealed that the approach in our case corresponds to standard procedure. The measured response allows conclusions about a long-term survival based on few available data. A therapy adjustment due to genetic findings based on the current data is not justified, especially if the response occurs to standard regimens.

Conclusions

The past has shown a different chemosensitivity of BRCA1/2 mutation-associated BC as compared to sporadic BC. Synergistic or additive effects of several combination therapies and the molecular mechanisms are not yet fully understood. So far, the available studies are mainly small and retrospective single-center analyses without mature follow-up data. These studies are hypothesis generating and help to direct further research, but are not sufficient to draw any firm conclusions for specific treatment recommendation or even to create specific guidelines for optimized chemotherapy of mutation carriers. Especially, the use of platinum-based regimens seems promising but warrants further evaluation in randomized clinical trials before allowing their routine application in patients with BRCA mutation. Larger prospective studies with optimized chemotherapeutic regimens are eagerly needed, in particular for a potentially curative disease setting such as adjuvant therapy or PST.

Disclosure Statement

There are no conflicts of interests (e.g. employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding) by any of the authors with regard to this paper.

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