Pathological complete response after primary chemotherapy in a mother and daughter with hereditary breast carcinoma: two case reports

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Summary

The prognosis of patients with BRCA1-related breast carcinomas is inferior to the patients without BRCA1 mutation, but most of these tumors have a so-called triple negative phenotype characterized by increased chemosensitivity. Information regarding the chemosensitivity of BRCA1-related breast carcinomas is limited. We present a case of a mother and daughter with hereditary breast carcinoma treated with primary chemotherapy using the dose-dense combination of doxorubicin and cyclophosphamide and sequential weekly paclitaxel administration. Pathological complete response was observed in both patients. Subsequent genetic analysis revealed the same BRCA1 mutation with exon 5-14 deletion in both women. The present experience as well as other reports indicate increased sensitivity of BRCA1-related breast carcinoma to primary chemotherapy.

Key words: Hereditary breast carcinoma; BRCA1; Pathological complete response.

Introduction

Breast cancer is the most common malignant disease of women in the Western world [1]. The progress accomplished in the treatment of breast cancer over the last decades is reflected in improved survival. In addition to early diagnosis, there is now strong evidence that much of the improvement in the prognosis of women with breast cancer is the result of systemic therapy, including hormonal treatment and chemotherapy [2].

Primary systemic (neoadjuvant or induction) therapy is currently the treatment of choice in locally advanced breast carcinoma, and the neoadjuvant approach is increasingly being used also in patients with operable tumors [3, 4]. Although both hormonal and cytotoxic drugs may be used in primary systemic therapy, chemotherapy with cytotoxic agents is in most cases the preferred modality as the activity of hormonal therapy is restricted to patients with tumors expressing hormone receptors, response onset is more rapid and response magnitude more pronounced with administration of cytotoxic agents. Currently, most regimens of primary systemic chemotherapy comprise anthracycline-based combinations with or without taxanes.

The term pathological complete response denotes complete disappearance of tumor cells in the operative specimen obtained at definitive surgery after primary chemotherapy [5]. Although instances of pathological complete response are relatively rare (for most regimens pathological complete response is achieved only in 10-20% of patients), pathological complete response is important as it represents the most significant prognostic parameter in women undergoing primary chemotherapy [6-9].

Hereditary breast carcinoma represents 5-10% of all cases of breast carcinoma. Most cases of hereditary breast carcinoma are caused by the mutations of BRCA1 or BRCA2 genes. A carrier of BRCA1 mutation carries a lifetime risk of breast carcinoma of about 80% and of epithelial ovarian carcinoma of about 50% [10]. The prognosis in patients with BRCA1-related breast carcinomas is inferior to the patients without BRCA1 mutations [11, 12], but patients with epithelial ovarian carcinoma harboring BRCA1 mutation have significantly better survival [13-15]. Most BRCA1-related breast carcinomas have a so-called triple negative phenotype, and triple negative breast carcinomas are characterized by increased chemosensitivity [16]. However, information on the chemosensitivity of BRCA1-related breast carcinomas is limited [17, 18].

We present two cases of pathological complete response after primary chemotherapy for breast carcinoma in a mother and her daughter, both carriers of BRCA1 mutations.

Case Reports

Case I

A 44-year-old woman presented in September 2003 with a 3-cm lump in the right breast and enlarged axillary lymph nodes. Biopsy confirmed poorly differentiated invasive breast carcinoma. On immunohistochemical examination, the tumor cells did not express estrogen receptors, progesterone receptors or HER-2, but the expression of Ki67 was extremely high (95%), and p53 was expressed in 40% of tumor cells. Because of the

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stage (T2N1M0) and phenotype of the tumor, primary chemotherapy with a dose-dense administration of four cycles of a combination of doxorubicin (60 mg/m2) and cyclophosphamide (600 mg/m2) was given every two weeks with filgrastim support, and subsequently 12 cycles of weekly paclitaxel (90 mg/m2) were indicated. The therapy was well tolerated and resulted in almost complete radiologic response. A partial mastectomy with exenteration of the axilla was performed on February 27, 2004. No tumor cells were detectable in the resection specimen, and pathological complete response was determined in the surgical specimen based on the Chevallier classification [5]. The patient was subsequently treated with adjuvant radiotherapy. At the last control in April 2007 the patient was without any signs of disease activity.

Case 2

A 26-year-old woman (daughter of the first case) observed a lump in her right breast during the last month of pregnancy. On September 2, 2004 she delivered a healthy female infant. During breastfeeding the patient observed enlargement of the lump and was referred for a biopsy. Lactation was interrupted. The biopsy revealed moderately differentiated invasive ductal carcinoma with no expression of estrogen or progesterone receptors, high expression of Ki67 (40-50 %), p53 (100%) and HER-2 (3+). At the time of diagnosis, the tumor was 3 cm in size, and there were no clinical or radiological signs of lymph node involvement (T2N0M0). Because of the high risk associated with the patient's age, the tumor size and phenotype, the patient was submitted to primary chemotherapy using the regimen outlined above. A partial response was detected after the completion of therapy, and a partial mastectomy with exenteration of the axilla was performed on June 22, 2005. A pathological complete response was detected in the surgical specimen with no residual tumor cells. The patient subsequently received adjuvant radiotherapy, and at the last control in April 2007 she was without signs of recurrence.

Molecular genetic analysis revealed the same BRCA1 mutation in both women (exon 5-14 deletion; g.21716_53298del 31583).

Discussion

The present observation of pathological complete response in a mother and daughter harboring the same BRCA1 mutation is in line with earlier reports of increased chemosensitivity of BRCA1-related carcinomas [13-15, 17, 18]. Due to the obvious difficulty associated with prospective assessment of response to chemotherapy in carriers of these relatively rare mutations, the data on this topic are limited to retrospective series. Among 615 women of Ashkenazi Jewish or French Canadian ancestry with known BRCA1/BRCA2 mutation status, Chappuis *et al*. [17] identified 37 breast carcinoma patients treated with primary chemotherapy, including 11 BRCA1/BRCA2 mutation carriers. Even in this cohort of limited size, the rate of clinical and pathological response was significantly higher in mutation carriers, and complete pathological response was observed in four out of nine (44%) evaluable patients harboring BRCA1/BRCA2 mutations compared to only one control case (4%). A single case of a BRCA1 positive patient with pathological complete response to primary chemotherapy has also been reported by Warner et al. [18]. In a retrospective series, presence of BRCA1 mutations in breast carcinoma patients was associated with inferior survival, but adjuvant chemotherapy significantly improved survival in BRCA1-positive patients [11, 12]. In contrast, the presence of a mutation in epithelial ovarian carcinoma, another BRCA1/BRCA1-related tumor with higher mortality and almost universal use of chemotherapy, is associated with markedly better survival [13-15]. Available experimental data also point out the generally increased chemosensitivity of BRCA1 mutant cells [19]. The BRCA1 protein is one of the molecules responsible for response to DNA damaging agents. BRCA1 protein participates in DNA repair, messenger RNA transcription, cell cycle regulation and protein ubiquitination, and the cells lacking BRCA1 protein are highly sensitive to alkylating agents, platinum derivatives and anthracyclines.

Currently, there is no universally accepted regimen for primary chemotherapy of breast carcinoma [3, 4]. The most important aim of primary chemotherapy, prolongation of patient survival, is identical with the aim of adjuvant chemotherapy. The trials of adjuvant chemotherapy in breast carcinoma have included a substantially higher number of patients than studies of primary chemotherapy, and survival benefit has been demonstrated in the adjuvant setting for the administration of anthracyclines [2], dose-dense approach [20], and the addition of taxanes [21], while trials of primary chemotherapy usually lacked statistical power to demonstrate a survival advantage. Based on earlier randomized clinical trials, the regimen used in both patients included dose-dense administration of the combination of doxorubicin and cyclophosphamide [20] as well as sequential weekly paclitaxel administration [22]. Among the agents administered to the two patients presented here, BRCA1 mutation has been associated with increased in vitro sensitivity to doxorubicin and alkylating agents, but relative resistance to paclitaxel [19]. Most BRCA1-related breast carcinomas are characterized by lack of estrogen and progesterone receptor expression as well by no increase of HER-2 expression (triple negative) [16]. In the present two cases, this triple negative phenotype was observed in the older patient (mother), while the younger patient (daughter) had estrogen and progesterone receptor-negative breast carcinoma with HER-2 overexpression. Trastuzumab was not used in this patient because at that time the results of studies demonstrating the survival benefit of this drug in an adjuvant setting were not available, and thus trastuzumab was not indicated.

The information on BRCA1 mutation status has so far had clinical significance restricted to the prevention of second primary tumors (most importantly contralateral breast carcinoma and epithelial ovarian carcinoma) in affected patients and to the genetic counseling of the relatives. The present observation illustrates genetic predisposition for chemosensitivity in BRCA1 mutation carriers and, along with other data, indicates that awareness of BRCA1 mutation status may be even more important for

the choice of therapy, including the decision of whether to administer primary chemotherapy. A marked response to primary chemotherapy allows breast-conserving surgery in patients indicated for mastectomy, and factors predictive of tumor response are of obvious importance in deciding whether to proceed to primary mastectomy or primary chemotherapy with the aim of breast conserving surgery.

Along with prolongation of survival and improvement of surgical options, the other aim of primary chemotherapy is the assessment of tumor response to a particular regimen in vivo, although the possibility of determining tumor response has so far been of little use in clinical practice. On the other hand, more widespread use of primary chemotherapy may lead to identification of patients in whom primary chemotherapy could be of benefit. Presently only retrospective and anecdotal data are available on increased chemosensitivity of BRCA1-related breast carcinomas, and additional information from prospective cohorts is needed.

In conclusion, the present two cases demonstrated increased sensitivity of BRCA1-related breast carcinoma to primary chemotherapy. The growing evidence of exquisite chemosensitivity of breast carcinoma in BRCA1 mutation carriers should affect the decision about primary chemotherapy in these patients.

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