A significant response to neoadjuvant chemotherapy in BRCA1/2 related breast cancer

P O Chappuis, J Goffin, N Wong, C Perret, P Ghadirian, P N Tonin, W D Foulkes

A significant response to neoadjuvant (preoperative) chemotherapy was initially developed as a first line treatment for locally advanced breast cancer. More recently, it has been used to treat earlier stage operable disease, with the hope that not only could the treatment be used as an in vivo assessment of tumour response, but also that it might more readily eradicate occult distant micrometastases. Many studies have shown a small but significant increase in breast conservation when neoadjuvant chemotherapy was used but, overall, most randomised studies have not shown any survival advantage following this treatment.\(^4\) Despite this, it has been noted that women receiving neoadjuvant chemotherapy who experience either a clinical complete response (cCR) (\(\leq 40\%\) of all those treated) or, more clearly, a pathological complete response (pCR) (\(\leq 10\%\)) have a better long term outcome than women who achieve less than a complete response.\(^1,2\)

Germline mutations in the *BRCA1* and *BRCA2* genes are the major genetic predisposition to breast cancer. Some of the functions of *BRCA1* and *BRCA2* proteins could be directly involved in response to cytotoxic agents, such as the role of *BRCA1/2* in DNA repair or apoptosis.\(^5,6\) Distinct pathological features and gene expression profiles suggest that there are differences in hereditary breast cancer compared to sporadic cases, which might lead to differences in treatment response. In vitro data suggest that cells without functional *BRCA1* or *BRCA2* protein are particularly sensitive to several chemotherapeutic drugs or ionising radiation.\(^7\) Mouse and human cell lines deficient in *BRCA1* or *BRCA2* display an increased sensitivity to agents causing double strand DNA breaks.\(^8,9\) This hypersensitivity has been shown for mitoxantrone, amsacrine, etopoide, doxorubicin, and cisplatin with a subsequent increased level of apoptosis.\(^10,11\) Differences in drug sensitivity might be explained by interaction of *BRCA1/2* proteins with various pathways leading to apoptosis.\(^12,13\) These findings raise the question of the efficacy of adjuvant chemotherapy or hormonotherapy for breast cancer among women who carry a germline *BRCA1/2* mutation.

**MATERIAL AND METHODS**

To address the question of initial response to chemotherapy for hereditary breast cancer, we reviewed all cases of Ashkenazi Jewish (AJ) or French Canadian (FC) women treated with neoadjuvant chemotherapy and for whom founder *BRCA1/2* mutation status had been determined through genetic testing facilities in Montreal, QC. We have a clinicopathological database of 615 AJ or FC women who have been tested for the known founder mutations in *BRCA1/2* that are present in these two populations.\(^15\) This testing was performed in both clinical and research settings between 1995 and 2001. By comparing this database with one containing women treated by neoadjuvant chemotherapy at McGill University or Université de Montréal hospitals, we identified 38 women (seven *BRCA1* mutation carriers (hereafter “carriers”), four *BRCA2* carriers, and 27 non-carriers) who developed histologically or cytologically diagnosed primary breast cancer (stages I-III) and received neoadjuvant treatment. Not carrying a germline *BRCA1/2* mutation was defined as follows: (1) for Ashkenazi Jewish patients (\(n=12\)), absence of the three *BRCA1/2* founder mutations\(^5\); and (2) for patients of French Canadian origin (\(n=15\)), absence of seven *BRCA1/2* founder mutations\(^6\) as well as a BRCAPRO score of \(<2\%\). One woman (J007) was identified as a *BRCA1* carrier 13 months before developing breast cancer and another (AJ32) was identified as a *BRCA1/2* non-carrier 17 months before her diagnosis. In all other cases, genetic testing was performed at or after breast cancer diagnosis. The period of time that elapses between breast cancer diagnosis and genetic testing was not statistically different among *BRCA1/2* carriers and non-carriers (median 0.5 year \(v\) 0.3 year, respectively, \(p=0.84\), Mann-Whitney U test).

The full clinicopathological details of the 38 subjects are shown in supplementary tables 1 and 2 (www.jmedgenet.com). Twenty-six out of 38 patients (6/11 carriers and 20/27 non-carriers, \(p=0.28\)) were included in prospective multicentre clinical trials that evaluated neoadjuvant treatment in breast cancer (NSABP-B18, -B26, and -B27, NCIC MA.10). Except for one patient (AJ32) treated with paclitaxel alone, all patients received anthracyclin based chemotherapy (usually four cycles) before surgery. After neoadjuvant treatment, all except two patients (1236 and 98120) underwent either a lumpectomy or segmental mastectomy with axillary lymph node dissection or a modified radical mastectomy. Clinical response was defined as: (1) complete response (CR), no residual palpable disease; (2) partial response (PR), \(\geq 50\%\) reduction in bidimensional measurements of the breast mass and axillary adenopathy; (3) no change, between 50% reduction and 25% increase in tumour size; or (4) progressive disease, \(>25\%\) increase in tumour size. As various regimens of neoadjuvant chemotherapy were administered, clinical response was systematically evaluated after three or four cycles of chemotherapy, and further clinical responses after any subsequent cycles were not included in any of our analyses (for full details, see supplementary tables 1 and 2). Pathological complete response (pCR) was recorded when there was no evidence of residual tumour cells in the breast and axillary lymph nodes. For the other cases, the pathological response was considered incomplete. No patient showed residual non-invasive (in situ) tumour cells without invasive component.

**RESULTS**

No significant difference was noted between carriers and non-carriers for age at diagnosis (mean (median) 44.1, SD 8.4 (43.4) years \(v\) 47.6, SD 11.4 (46.2) years, \(p=0.37\)), tumour size (mean (median) 5.5, SD 2.6 (6.0) cm \(v\) 4.9, SD 3.0 (4.0) cm, respectively). No significant difference was noted between carriers and non-carriers for oestrogen receptor (ER) and progesterone receptor (PR) status (mean (median) ER 65.7% (64%) \(v\) 63.2% (63%), \(p=0.75\); mean (median) PR 94.9% (95%) \(v\) 94.1% (94%), \(p=0.65\)). When carriers were compared with non-carriers, no significant difference was noted between carriers and non-carriers for the following clinicopathological variables: tumour grade (mean (median) 2.7 (3) \(v\) 2.6 (3), \(p=0.61\)), number of positive nodes (mean (median) 3 (2) \(v\) 3 (2), \(p=0.15\)), and completeness of surgical excision (mean (median) 99.4% (100%) \(v\) 98.7% (100%), \(p=0.15\)).

**Abbreviations:** AJ, Ashkenazi Jewish; FC, French Canadian; cCR, clinical complete response; pCR, pathological complete response; CR, complete response; PR, partial response; ER, oestrogen receptor.
p=0.52), oestrogen receptor (ER) status (p=0.23), or tumour grade (mean (median) 2.6, SD 0.50 (3) v 2.4, SD 0.76 (3), p=0.44) (supplementary tables 1 and 2). After three or four cycles of neoadjuvant chemotherapy, a cCR was recorded in 10 of 11 BRCA1/2 carriers (93%) compared with eight of 27 non-carriers (30%), p=0.0009 (table 1A). Notably, four (two BRCA1 carriers and two BRCA2 carriers) of nine (44%) evaluable BRCA1/2 carriers had no residual tumour in the breast and the axillary lymph nodes (pCR), whereas only one case of pCR (4%) was noted among the non-carriers (p=0.009, table 1B). When we matched the cases 1:1 to controls on precise TNM stage, the significance of the effect of mutation status on complete clinical response rate was slightly less marked (table 1A), reflecting the smaller sample size. Similarly, when we analysed pCR in the matched series of 18 carriers and non-carriers, the effect diminished and is of borderline statistical significance (table 1B).

**DISCUSSION**

We report here preliminary evidence for a differential response to neoadjuvant chemotherapy for breast cancer on the basis of germline BRCA1/2 mutation status. BRCA1/2 carriers showed a better clinical response rate to neoadjuvant chemotherapy than did non-carriers. Importantly, the clinical and pathological responses to neoadjuvant treatment observed in BRCA1/2 non-carriers were concordant with what has been reported previously. The probability of a CR appears to be independent of clinical stage and grade. The two carriers who had a clinical complete response were excluded from this analysis because they did not have any further surgery after neoadjuvant chemotherapy.

In the unmatched analyses, we did not observe significant differences for age at diagnosis, ER status, or tumour grade among carriers and non-carriers, although some non-significant differences were noted. It is possible that the small sample size and the younger than expected age of the controls accounts for this finding. Whatever the reason for the lack of difference, the clinical and pathological characteristics of the breast cancers occurring in carriers and non-carriers, whether matched or unmatched, suggests that such potential differences are unlikely to explain the results we observed, particularly as a statistically significant difference in clinical response rates was observed when close matching was performed.

Another possibility is that pCR was preferentially achieved by carriers because they received more chemotherapy before pathological confirmation of response. However, only one carrier with pCR received more than four cycles of neoadjuvant chemotherapy, and this woman (J322, supplementary table 1) had achieved a cCR after four cycles of doxorubicin and cyclophosphamide. Moreover, five non-carriers (supplementary table 2) received more than four cycles of neoadjuvant chemotherapy without achieving a pCR, so it does not appear that adding further chemotherapy after the fourth cycle is the reason why, overall, carriers were statistically significantly more likely to achieve pCR than were non-carriers.

As stated above, the breast cancers occurring in BRCA1/2 carriers and non-carriers did not significantly differ in terms of standard clinicopathological variables. It is therefore tempting to speculate that it is the presence of the germline BRCA1/2 mutation per se that is determining the difference in response to neoadjuvant chemotherapy. Considering outcome, women who have a cCR and/or pCR have a better long term outcome than women who do not achieve a CR. Presumably, those who achieve CR are more likely to have eliminated micrometastases. We and others previously showed that BRCA1/2 mutation status is associated with a worse outcome after invasive breast cancer. This apparent paradox of a very good initial response to preoperative chemotherapy among carriers and a worse long term survival needs further study. Of note, no survival studies have been stratified according to the administration of adjuvant chemotherapy. Among a cohort of 292 Ashkenazi Jewish women diagnosed with invasive breast cancer between 1980 and 1995, we recently showed that the overall survival was significantly worse among BRCA1 mutation carriers compared to non-carriers, but only among patients who did not receive adjuvant chemotherapy.

Putting our two observations together, one might speculate that the poor survival observed in some retrospective series is partly explained by the omission of chemotherapy in these historical series, and that
this might have been ameliorated by adjuvant chemotherapy. Therefore, as little is known about the in vivo response of BRCA1/2 related breast cancer to chemotherapeutic agents, it will be important to establish whether the very promising initial response to neoadjuvant chemotherapy we observed in BRCA1/2 carriers will be sustained. Larger, prospective studies will be required to confirm or refute our preliminary observations.

ACKNOWLEDGEMENTS

We thank Ann-Josée Paradis, Nancy Hamel, Karlene Austraile, Lidia Kasprzak, and Muna Al-Saffar for technical assistance. POC was funded by a fonds de perfectionnement of the University Hospital of Geneva, Geneva, Switzerland. PNT is a recipient of a Fraser, Monat and McPherson Scholarship and the Stewart Fellowship in Research/ Clinical Hematology and Oncology. WDF is a recipient of a Fonds de Recherche en Santé du Québec (FRSQ) Clinician Scientist J2 Fellowship. This work was supported in part by grants from the Department of Defense (No DAMD17-98-1-8112), the FRSQ (FRSQ-Réseau cancer: Axe Cancer du Sein et de l’Ovaire), the Canadian Breast Cancer Foundation, the CURE foundation, and the Canadian Genetic Diseases Network.

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Authors’ affiliations

P O Chappuis†, Division of Medical Genetics, Department of Medicine, McGill University Health Centre, Montreal, Quebec, Canada

J Goffin, Department of Oncology, McGill University, Montreal, Quebec, Canada

N Wong, Cancer Prevention Research Unit and Department of Medicine, Sir M B Davis-Jewish General Hospital, McGill University, Montreal, Quebec, Canada

C Perret, P Ghadriari, Epidemiology Research Unit, Research Centre, CHUM-Hôtel Dieu Faculty of Medicine, University of Montreal, Montreal, Quebec, Canada

P N Tonin, W D Foulkes, Program in Cancer Genetics, Departments of Oncology and Human Genetics, Research Institute of the McGill University Health Centre and Department of Medicine, McGill University, Montreal, Quebec, Canada

Correspondence to: Dr W D Foulkes, Montreal General Hospital/Room L10-120, 1650 Cedar Avenue, Montreal, Quebec H3G 1A4, Canada; william.foulkes@mcgill.ca

*Present address: Divisions of Oncology and Medical Genetics, University Hospital, Geneva, Switzerland.

REFERENCES


Supplementary tables 1 and 2 can be found on the journal website at www.jmedgenet.com.

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