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Germline *BRCA* mutation does not prevent response to taxane-based therapy for the treatment of castration-resistant prostate cancer

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Abstract

- To investigate the relationship between *BRCA* mutation status and response to taxane-based chemotherapy, since *BRCA* mutation carriers with prostate cancer appear to have worse survival than non-carriers and docetaxel improves survival in patients with castration-resistant prostate cancer.
- We determined *BRCA* mutation prevalence in 158 Ashkenazi Jewish (AJ) men with castration-resistant prostate cancer. Clinical data were collected as part of an institutional prostate cancer research database and through additional medical record review.
- Clinical records and DNA samples were linked through a unique identifier, anonymizing the samples before genetic testing for the AJ *BRCA1/2* founder mutations.
- Response to taxane-based therapy was defined by the prostate-specific antigen nadir within 12 weeks of therapy.
- In all, 88 men received taxane-based treatment, seven of whom were *BRCA* carriers (three *BRCA1*, four *BRCA2*; 8%). Initial response to taxane was available for all seven *BRCA* carriers and for 69 non-carriers.
- Overall, 71% (54/76) of patients responded to treatment, with no significant difference between carriers (57%) and non-carriers (72%) (absolute difference 15%; 95% confidence interval –23% to 53%; $P = 0.4$).
- Among patients with an initial response, the median change in prostate-specific antigen was similar for *BRCA* carriers (–63%, interquartile range –71% to –57%) and non-carriers (–60%, interquartile range –78% to –35%) ($P = 0.6$).
- At last follow-up, all seven *BRCA* carriers and 49 non-carriers had died from prostate cancer. One *BRCA2* carrier treated with docetaxel plus platinum survived 37 months.

- In this small, hypothesis-generating study approximately half of *BRCA* carriers had a prostate-specific antigen response to taxane-based chemotherapy, suggesting that it is an active therapy in these individuals.

Keywords

castration-resistant prostate cancer; *BRCA1*; *BRCA2*; taxane; docetaxel; response

Introduction

Germline *BRCA* mutations are associated with an increased risk of prostate cancer and appear to predict aggressive disease with carriers showing earlier progression through the prostate cancer clinical states model and increased prostate-cancer-specific mortality than non-carriers [1–5]. The inferior outcome in *BRCA* carriers with prostate cancer contrasts with the improved outcome reported in *BRCA*-associated ovarian cancer [6–9] and with the similar outcomes seen in carriers and non-carriers with breast cancer [10].

BRCA1 and *BRCA2* are implicated in many pathways that contribute to DNA repair [11], a function that may explain the differential outcome for carriers and non-carriers. It has been proposed that double-strand DNA breaks, acting through the androgen receptor, produce the TMPRSS2–ERG gene fusion that is found in 50% of prostate cancer [12,13]. Androgen signalling appears to induce proximity of the TMPRSS2 and ERG genomic loci, and in one study radiation-induced DNA double-strand breaks then facilitated the TMPRSS2–ERG gene fusion [12]. This gene fusion has been associated with aggressive disease, and it is possible that, in the absence of *BRCA*, accumulating double-strand breaks facilitate this translocation. A pharmacogenetic effect whereby germline *BRCA* mutation alters the efficacy of some agents but not of others may also explain the opposing prognostic reports of *BRCA* status in cancers treated with different agents.

Preclinical and clinical data consistently show increased platinum sensitivity among *BRCA1* and *BRCA2* mutation carriers with ovarian cancer [14], and a similar effect has been reported in breast cancer [15]. It has been proposed that response to taxanes requires functional *BRCA1* which activates the mitotic checkpoint and induces apoptosis [16–20]; however, the chemo-modulatory effect of *BRCA* status on taxane sensitivity is not known. Inhibition of *BRCA1* in ovarian and breast cancer cell lines has been reported to decrease the apoptotic response to docetaxel and paclitaxel leading to increased chemo-resistance [17]. In contrast, two ovarian cancer cell line studies suggest that increased *BRCA1* expression confers increased sensitivity to paclitaxel [21,22]. Clinical data in this setting are very limited with only two small breast cancer studies suggesting that *BRCA1*-associated breast cancer is less responsive to taxanes [23,24]. An association between *BRCA2* mutation status and response to taxanes has not been reported.

Docetaxel is the only treatment that leads to an improvement in survival in men with castration-resistant prostate cancer (CRPC) [25]. We investigated whether *BRCA1/2* mutation status conferred resistance or sensitivity to taxane-based therapy in patients with advanced prostate cancer.

Patients and Methods

The case records of 832 Ashkenazi Jewish men treated for localized prostate cancer at Memorial Sloan-Kettering Cancer Center (MSKCC) between June 1988 and December 2007 were reviewed to identify a subset of this population who developed metastatic CRPC. Castration-resistant metastatic disease was defined as progression of disease following androgen deprivation therapy. In all, 158 patients were identified and blood samples

provided by these men were genotyped for germline *BRCA1* and *BRCA2* mutations. The inclusion of only Ashkenazi Jewish men allowed for targeted genotyping for founder mutations with all blood samples genotyped for the two major Ashkenazi *BRCA* founder mutations *BRCA1**185delAG and *BRCA2**6174delT. Genotyping was not performed for the *BRCA1**5382insC founder mutation. The TaqMan™ (fluorogenic 5' nuclease) assay was used for SNP genotyping. The primers and probes were obtained from Applied Biosystems (Foster City, CA, USA). PCR was conducted with both primers and probes added in the ABI 9700 thermocycler, and the endpoint results were scored using the ABI 7900HT Sequence Detection System (version 2.3). In each 384-well plate, one reference sample and one negative control were included for quality control.

Cases' medical records and pathology reports were collected as part of an institutional prostate cancer research database using standardized questionnaires and chart abstraction forms, created and maintained by the prostate cancer disease management team at MSKCC. In addition, each chart was reviewed by a single physician to confirm existing data and gather additional information regarding disease progression and response to treatment. Clinical records and DNA samples were linked through a unique identifier. In accordance with an institutional research board approved protocol, the link between patient information and the identifier was destroyed once clinical data were abstracted, thereby anonymizing the samples before germline analysis. For men with CRPC, data were collected regarding parameters at the start of taxane-based therapy including age, PSA, lactate dehydrogenase, haemoglobin, alkaline phosphatase, albumin, Karnofsky performance status and year of treatment. At the time of diagnosis clinical stage and biopsy score in addition to initial treatment were recorded. Analysis was based on PSA values within 12 weeks of treatment and cause of death. Response to taxane-based therapy was assessed using the maximum decline within a 12-week period after initiation of treatment.

Statistical Methods

The proportion of patients with an initial PSA response to taxane-based therapy was compared between carriers and non-carriers using Fisher's exact test. In the subgroup of patients with an initial response to taxane-based therapy, the percentage change in PSA (calculated as 100 times the lowest PSA within 12 weeks of treatment start, divided by PSA at treatment start) was compared between carriers and non-carriers using the Mann–Whitney test. Survival from the start of treatment was summarized descriptively. Survival was not compared formally between carriers and non-carriers because of the limited number of *BRCA* carriers. Statistical analyses were conducted using Stata 10.1 (StataCorp LP, College Station, TX, USA).

Results

After a median follow-up in excess of 8 years, 156 men from the original cohort of 832 individuals with localized prostate cancer developed castration-resistant metastatic disease, and 76 of these patients were evaluable for response to taxane-based therapy. Treatment regimens for these 76 patients included single-agent docetaxel ($n = 33$ patients), docetaxel + estramustine (17 patients), docetaxel + samarium (five patients), docetaxel + bevacizumab (four patients), docetaxel + 17AAG (two patients), docetaxel + DN-101 (two patients), docetaxel + carboplatin (one patient), docetaxel + trastuzumab (one patient), docetaxel + cyclophosphamide (one patient), paclitaxel (three patients), paclitaxel + carboplatin + estramustine (six patients) and paclitaxel + estramustine (one patient). Seven of 88 patients were *BRCA* carriers (three *BRCA1*, four *BRCA2*; 8%).

Patient characteristics according to *BRCA* carrier status are shown in Table 1. At the time of initiating taxane-based therapy, *BRCA* carriers had higher PSA, lactate dehydrogenase and alkaline phosphatase levels. The *BRCA* carriers also had higher biopsy Gleason scores at diagnosis; however, primary treatment approaches were similar in both groups.

Initial PSA response to taxanes was available for all seven *BRCA* carriers and for 69 non-carriers. Overall, 71% (54/76) of patients responded to taxanes (Table 2). Four (one *BRCA1*, three *BRCA2*) out of seven *BRCA* carriers (57%) had a PSA response. In the subgroup of patients who responded, the median change in PSA level among four *BRCA* carriers was -63%; all these patients had a >50% decrease in PSA. Among non-carriers, the proportion of patients who responded to docetaxel was similar (73%, 50/69), as was the median change in PSA level in the subgroup of 50 non-carriers who responded (-60%, interquartile range -78% to 35%). There was no significant difference in the proportion of responders among *BRCA* carriers and non-carriers ($P = 0.4$), nor in the percentage change in PSA level among responders between the groups ($P = 0.6$). After a median follow-up of 8 years, all the seven *BRCA* carriers had died from prostate cancer, compared with 49 non-carriers (Table 3). One *BRCA2* carrier treated with docetaxel plus platinum survived 37 months. Among the 81 non-carriers, only 10 (12%) were alive and followed past 36 months.

There were 60 deaths overall, and 53 in the subgroup of 76 evaluable patients for initial response to docetaxel. Kaplan–Meier survival probabilities according to response status are given in Fig. 1. Median survival was 25 months for patients with >50% response, 15 months for patients with a 1–50% response and 21 months for patients without an initial response ($P = 0.4$ by log-rank test).

Discussion

In this cohort of men with CRPC, *BRCA* mutation carriers had similar rates of PSA response to treatment and similar absolute reductions in PSA value to non-carriers. Despite preclinical data suggesting that *BRCA* (particularly *BRCA1*) mutation acts as a modulator of response to chemotherapy in ovarian and breast cancer cell lines [16–20], *BRCA* mutation did not appear to confer resistance to taxanes in men with CRPC. A low rate of pathological complete response was recently observed in female *BRCA1* mutation carriers with breast cancer treated with neoadjuvant doxorubicin plus docetaxel (response rate 8%) [15]. In contrast, another study including 12 women treated with neoadjuvant cisplatin showed an 83% response rate, suggesting that the modulatory effect of *BRCA* mutation status on response to chemotherapy may be agent specific. Docetaxel (75 mg/m² every 3 weeks) plus prednisolone (5 mg twice a day) is the standard of care for the treatment of CRPC based on two randomized trials showing a significant improvement in overall survival for the combination compared with mitoxantrone plus prednisolone [25,26]. Despite preclinical data suggesting that the presence of a *BRCA1* mutation may predict resistance to taxanes, the present small study does not support the hypothesis that *BRCA* mutation status overall acts as a modulator of response to these agents.

Our use of PSA decline as an endpoint in the present study was mandated by its retrospective design. A decline of 50% was previously suggested as a measure of efficacy [27]; however, the subsequent Prostate Cancer Clinical Trials Working Group clearly outlined the inadequacy of early changes in PSA as the sole endpoint in trials investigating novel therapies for CRPC, and emphasized the additional importance of time-to-event endpoints which more meaningfully reflect the clinical impact of treatment. A retrospective review of men with androgen-independent prostate cancer treated with either docetaxel/estramustine or mitoxantrone/prednisone on Southwest Oncology Group Protocol 99-16 suggested that PSA decline is a surrogate for survival [28,29]. Three-month PSA level

declines of 20–40%, a 2-month PSA decline of 30%, and PSA velocity at 2 and 3 months were all surrogates for survival in this retrospective cohort. PSA declined by >50% in all four *BRCA* mutation carriers treated with docetaxel in the present study, and we could therefore only assess a 50% decline as a measure of PSA response. Our survival analysis was limited by small numbers but greater PSA decline was not significantly associated with improved survival ($P = 0.4$), again emphasizing the recommendations of the Prostate Cancer Clinical Trials Working Group and the importance of time-to-event endpoints.

BRCA-associated prostate cancer represents a genetically defined subset of the disease that may be more sensitive to platinum-based chemotherapy. Platinum agents, such as cisplatin and carboplatin, have moderate single-agent activity in CRPC [30–33]. Carboplatin has been combined with estramustine and a taxane (docetaxel or paclitaxel) in a number of phase II studies with PSA decline 50% seen in 60–100% of patients and objective response rates from 45–65% in patients with measurable disease, although it is difficult to separate the effect of carboplatin from that of the taxane used in these studies [34–40]. In a recent phase III study, the oral platinum agent satraplatin delayed progression of disease and pain in patients with metastatic CRPC experiencing progression after initial chemotherapy [41]. An overall survival benefit was not shown in this study although tailoring therapy to a group more likely to respond, such as *BRCA* mutation carriers, may have resulted in a different outcome. *BRCA* mutation status appears to predict response to platinum-based therapy for patients with ovarian and breast cancer and may do the same for men with prostate cancer [14,15,24]. The one *BRCA2* carrier treated with docetaxel plus carboplatin in our study survived 37 months, more than twice the survival of other mutation carriers. Using the MSKCC nomogram for patients with hormone refractory disease which does not include *BRCA* status as a variable, this man's expected median overall survival was 20 months. It is possible that the use of carboplatin overcame the reported poor prognostic association between *BRCA* mutation and prostate-cancer-specific survival, suggesting a potential role for carboplatin in this setting.

Inhibitors of poly-ADP ribose polymerase 1 (PARP1) offer an additional therapeutic option for *BRCA* carriers with reported efficacy in *BRCA*-associated breast and ovarian cancer [42,43]. PARP1 is a constitutively expressed nuclear enzyme important in base excision repair of single-stranded DNA breaks [44]. In its absence excessive single-strand breaks accumulate, leading to collapsed DNA replication forks and conversion of single-strand breaks to double-strand breaks. *BRCA1* and *BRCA2* proteins repair double-strand DNA breaks by homologous recombination, and *BRCA*-defective cells are unable to repair these double-strand breaks, resulting in tumour cell death [45,46]. Inhibition of PARP1 in *BRCA*-deficient cells uses the concept of synthetic lethality whereby a mutation in either of two genes individually has no effect on cell survival but combining the mutations leads to cell death. Loss of the tumour suppressor gene phosphatase and tensin homologue (*PTEN*) also results in impaired homologous recombination, and tumours deficient in *PTEN* may also be sensitive to PARP1 inhibition [47]. Prostate cancer is not a recognized manifestation of Cowden syndrome, an autosomal dominant condition caused by germline mutations in *PTEN*, and common genomic variation at *PTEN* does not appear to increase risk of prostate cancer, but studies of somatic mutations in prostate cancer report *PTEN* abnormalities. In one study 63% of radical prostatectomy specimens had heterozygous loss of *PTEN* using fluorescent *in situ* hybridization [48], although studies looking at *PTEN* mutation report lower proportions. Homozygous deletions of *PTEN* have been detected in up to 15% of locally confined cancers and up to 30% of metastases. Heterozygous loss has been reported in 13% of locally confined cancers and up to 39% of metastases [49–53]. A phase II study of a PARP inhibitor with temozolomide for the treatment of prostate cancer recently opened, and PARP inhibition of *BRCA*-associated prostate cancer and possible *PTEN*-deficient disease is worth further investigation.

BRCA1 and *BRCA2* mutation carriers have a reported threefold increased risk of developing prostate cancer [1,2]. Given the estimated 0.0069 *BRCA2* mutation frequency in the population, this translates to $\approx 2\%$ of the 180 000 prostate cancer cases in the USA attributable to *BRCA2* mutations, or 3600 cases each year which could benefit from treatments tailored to *BRCA2* status. Treatment of *BRCA*-associated prostate cancer with PARP inhibition would represent a first step towards the personalized management of this disease. As emphasized by three recent studies of PARP inhibition in *BRCA*-associated cancers a cooperative multi-institution approach facilitated rapid accrual [42,43,54]. Of the 171 participants in these studies, only 12% (20 patients) were male and it is likely that male family members of female probands in families with the hereditary breast ovarian cancer syndrome would willingly participate in future studies investigating targeted therapy for *BRCA*-associated prostate cancer.

As this is a small study of only seven *BRCA* mutation carriers, it must be viewed as hypothesis generating. We grouped *BRCA1* and *BRCA2* mutation carriers together despite the absence of preclinical data suggesting that *BRCA2* predicts resistance to taxanes. Nonetheless, our results illustrate that both *BRCA1* and *BRCA2* mutation carriers may respond to taxane-based therapy. The retrospective design of the present study limits interpretation of the results, not only because of the nature of the endpoints evaluated but also because we included different taxane-based regimens in our analysis. It is unknown if combination regimens could alter the predictive potential of *BRCA1*, although all *BRCA1* carriers in the present study received single-agent docetaxel.

BRCA-associated prostate cancer represents a genetically defined subset of the disease associated with worse outcome [55]. As such *BRCA* mutation may be considered a biomarker for aggressive prostate cancer. We report that it is possible for *BRCA*-associated prostate cancer to respond to taxane-based therapy, with no suggestion of resistance based on *BRCA* status. One *BRCA* mutation carrier achieved prolonged survival with platinum-based treatment. Platinum chemotherapy and PARP inhibition are active in *BRCA*-associated breast and ovarian cancer and are worth investigation in *BRCA*-associated prostate cancer.

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Abbreviations

CRPC	castration-resistant prostate cancer
MSKCC	Memorial Sloan-Kettering Cancer Center
PARP1	poly-ADP ribose polymerase 1
<i>PTEN</i>	phosphatase and tensin homologue

Number at risk					
>50% response	32	25	13	5	1
1-50% response	22	13	5	2	1
No response	22	12	7	2	1

FIG. 1. Overall survival stratified by initial response to docetaxel (n = 76)

Table 1
Patient characteristics for men treated with taxane-based chemotherapy for CRPC

	<i>BRCA</i> carrier	
	Yes, <i>N</i> = 7	No, <i>N</i> = 81
Characteristics at start of docetaxel treatment		
Age (median, range)	72 (59, 82)	75 (69, 79)
PSA level	199 (3, 811)	73 (18, 262)
Haemoglobin	12 (11, 13)	12 (10, 13)
LDH	259 (196, 480)	191 (155, 231)
Alkaline phosphatase	272 (132, 446)	91 (64, 169)
Albumin	4.1 (3.8, 4.4)	4.2 (3.9, 4.4)
KPS		
70	2 (28%)	6 (8%)
80	5 (72%)	68 (92%)
Characteristics of initial prostate cancer diagnosis		
Clinical stage		
T1	1 (14%)	11 (14%)
T2	3 (43%)	21 (26%)
T3	2 (29%)	22 (27%)
T4	0 (0%)	3 (4%)
Unknown	1 (14%)	24 (30%)
Biopsy Gleason score		
6	1 (14%)	13 (16%)
7	3 (43%)	28 (35%)
8	0 (0%)	19 (23%)
9	3 (43%)	19 (23%)
Unknown	0 (0%)	2 (2%)
Primary treatment		
Prostatectomy	3 (43%)	39 (48%)
Radiotherapy alone	1 (14%)	22 (27%)
Radiotherapy + ADT	2 (29%)	12 (15%)
Hormones alone	1 (14%)	7 (9%)
Watchful waiting	0 (0%)	3 (4%)
Chemotherapy	0 (0%)	1 (1%)
<i>BRCA</i> carrier status		
<i>BRCA1</i> +	3 (43%)	0 (0%)
<i>BRCA2</i> +	4 (57%)	0 (0%)

LDH, lactate dehydrogenase; KPS, Karnofsky performance status; ADT, androgen deprivation score.

Table 2
PSA response to taxane-based treatment

	BRCA carrier		<i>P</i>
	Yes, <i>N</i> = 7	No, <i>N</i> = 69	
Initial response to taxane (<i>n</i> = 76)			
Yes (>50% decline)	4 (57%)	28 (42%)	0.5
Yes (31–50% decline)	0 (0%)	14 (20%)	
Yes (1–30% decline)	0 (0%)	8 (12%)	
No	3 (43%)	19 (28%)	
Subgroup with initial response (<i>n</i> = 54)			
PSA level at treatment start	44, 1.8, 250, 811 *	86 (23, 262)	
Lowest PSA level within 12 weeks of treatment start	20, 0.7, 88, 179 *	25 (7, 109)	
Percentage change in PSA level	–53, –62, –64, –78 *	–60 (–78, –35)	0.6

* Actual values for the four *BRCA* carriers with an initial response. The median percentage change in PSA level for the four *BRCA* carriers was –63%.

Table 3

Treatment details for the seven BRCA carriers studied

Patient	BRCA	Age (years)	Treatment	Response	PSA level at treatment start	PSA nadir within 12 weeks	% change in PSA level	Treatment to death (months)
1	1	77	D	No	3	8	220	4.1
2	1	82	D	Yes	44	20	-53	16.9
3	1	88	D	No	199	294	48	2.1
4	2	59	D	Yes	811	179	-78	8.1
5	2	64	D+carboplatin	Yes	2	1	-62	37
6	2	78	D+estramustine	No	1110	1115	0.5	10.1
7	2	72	D	Yes	250	88	-65	17.4

D, docetaxel.