Patterns and duration of primary and recurrent treatment in ovarian cancer patients with germline BRCA mutations

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1. Introduction

Approximately 15% of epithelial ovarian cancers (OC) are associated with germline BRCA1 and BRCA2 (BRCA) mutations (Norquist et al., 2016). Patients with OC and germline BRCA mutations differ from sporadic cases in both tumor biology and treatment response. Women with BRCA1 mutations present with OC at an earlier age (Alsop et al., 2012; Yang et al., 2011), and both BRCA1 and BRCA2 carriers usually have high-grade tumors (Norquist et al., 2016; Alsop et al., 2012). BRCA mutation carriers with OC, especially BRCA2 carriers, have better five year survival rates than their counterparts without BRCA mutations (Norquist et al., 2016; Alsop et al., 2012; Yang et al., 2011; Bolton et al., 2012; Pennington et al., 2014; Tan et al., 2008; Ben David et al., 2002). This is in part due to increased platinum sensitivity and longer progression-free intervals (Alsop et al., 2012; Yang et al., 2011; Pennington et al., 2014). In addition, BRCA carriers have OCs that can be particularly sensitive to polyadenosine ribose polymerase (PARP) inhibitors (Fong et al., 2009). Despite these differences in tumor biology and clinical behavior, less is known about the long-term disease course (beyond five years) of OC patients with germline BRCA mutations. Chetrit et al. (Chetrit et al., 2008) demonstrated improved survival rates for women with BRCA mutations relative to wildtype controls with up to eight years of follow-up. However, recent studies suggest that the initial survival benefit seen in BRCA carriers disappears after ten years, though those data precede widespread access to PARP inhibitors (Kotsopoulos et al., 2016).

Due to the apparent unique features of germline BRCA-mutated OC, there is a need for information on the treatment patterns and outcomes over long-term periods of follow-up in this group. To our knowledge, there are no existing data on how much time women with BRCA mutations spend on treatment versus off treatment after an OC diagnosis and how many lines of therapy they typically receive, which reflect treatment burden. The objective of this study was thus to describe the disease course of a cohort of unselected OC patients with germline BRCA mutations, with an emphasis on treatment type, treatment duration, and disease status. Our goals are to present a comprehensive description of the natural history of germline BRCA mutation associated OC and provide information that can be useful for patient counseling. These baseline data are useful as women debate the merits of frontline or secondary maintenance therapy with PARP inhibitors, which is the
new frontier of OC treatment for women with BRCA mutations (Moore et al., 2018; Pujade-Lauraine et al., 2017).

2. Methods

Patients with Stage II or higher, high-grade epithelial OC harboring germline BRCA mutations were retrospectively identified from an IRB-approved institutional tissue bank from 2004 to 2014. All patients in the tissue bank had provided informed consent. Banked DNA samples were sequenced using BROCA, a targeted capture, massively parallel sequencing test developed at the University of Washington, Seattle, as previously described (Walsh et al., 2010). Women were excluded if complete medical records and adequate follow-up (at least 3 years after diagnosis or until death) were not available, if they carried a BRCA variant of uncertain significance, or if they were diagnosed with an occult cancer at the time of risk-reducing salpingo-oophorectomy.

Demographic, pathological, treatment and outcome data were abstracted by review of medical records. Treatment information included use of neoadjuvant chemotherapy, debulking surgery, and adjuvant chemotherapy for all patients. For patients who recurred, date of recurrence and details of each subsequent treatment were collected. Operations performed by a gynecologic oncologist for the purpose of OC cytoreduction were considered debulking surgeries and were categorized as complete (no residual disease), optimal (≤1 cm residual disease) or suboptimal (>1 cm residual disease). Women were considered to have received intraperitoneal chemotherapy if at least one cycle was administered intraperitoneally. Maintenance therapy was defined as the initiation or continuation of a chemotherapy agent after a complete or partial response was achieved.

Platinum free interval (PFI) was defined as the number of months elapsed from the last day of platinum chemotherapy for first-line treatment to the date of diagnosis of disease recurrence, or date of last follow-up if the patient did not recur during the study period. Patients were considered to have platinum-sensitive disease if the PFI was ≥ 6 months, platinum-resistant disease if the PFI was < 6 months, and platinum-refractory disease if they did not respond at least partially to first-line platinum therapy. Median overall survival was calculated from date of diagnosis to date of death and censored at last patient contact, as well as from the date of first recurrence until date of death or last patient contact. The proportion of time on cytotoxic chemotherapy was calculated by adding each interval during which a patient received cytotoxic chemotherapy, and dividing this by the total amount of time elapsed from diagnosis to death or date of last contact. Similarly, the proportion of time spent on any cancer-directed therapy was calculated by adding each interval during which a patient had received any form of cancer-directed therapy and dividing this by the total amount of time. Cancer-directed therapy included any chemotherapy (neoadjuvant, adjuvant and maintenance), surgery and radiation, but excluded hospice and palliative-only care.

We calculated descriptive statistics as frequencies and proportions and compared characteristics between groups using t-tests for continuous data and chi-square tests or Fisher’s exact tests for categorical data. Survival times were calculated using the Kaplan-Meier method and differences in median survival between groups were compared using log-rank test. P-values < .05 were considered statistically significant. We created a Swimmer’s Plot to depict individual disease timelines.

3. Results

Forty patients with Stage II-IV, high-grade epithelial OC and deleterious germline BRCA mutations (n = 26 BRCA1; 14 BRCA2) with complete medical records and adequate follow-up were available for review. The mean age at diagnosis was 54 years (range: 32–77) for the entire cohort and was younger for BRCA1 mutation carriers (52 years) compared to BRCA2 mutation carriers (57 years, p-value = .06). Most patients were white, had Stage IIIIC disease, and had tumors with serous histology. Patient characteristics are summarized in Table 1.

| Table 1 | Baseline characteristics of 40 patients with OC and germline BRCA mutations. Percentages are calculated per column and may not add to 100% due to rounding. |
| --- | --- | --- | --- | --- |
| All (n = 40) | BRCA1 (n = 26) | BRCA2 (n = 14) | p-value |
| Age | | | | |
| < 35 | 1 (2) | 1 (4) | 0 (0) | 0.206 |
| 35–45 | 3 (8) | 3 (12) | 0 (0) |
| 41–45 | 3 (8) | 3 (12) | 0 (0) |
| > 45 | 33 (82) | 19 (73) | 14 (100) |
| Race/ethnicity | | | | 0.950 |
| White | 32 (80) | 19 (73) | 13 (93) |
| Black | 1 (2) | 1 (4) | 0 (0) |
| Hispanic (any race) | 3 (8) | 2 (8) | 1 (7) |
| Asian | 1 (2) | 1 (4) | 0 (0) |
| Native American | 2 (5) | 2 (8) | 0 (0) |
| Multiracial | 1 (2) | 1 (4) | 0 (0) |
| Year of diagnosis | | | | 0.763 |
| 2004–2008 | 17 (42) | 12 (46) | 5 (36) |
| 2009–2014 | 23 (57) | 14 (54) | 9 (64) |
| Stage | | | | 0.594 |
| Untaged | 1 (2) | 1 (4) | 0 (0) |
| II | 1 (2) | 1 (4) | 0 (0) |
| IIIA-B | 4 (10) | 3 (12) | 1 (7) |
| IIIC | 25 (62) | 14 (54) | 11 (79) |
| IV | 9 (22) | 7 (27) | 2 (14) |
| Histology | | | | 0.401 |
| Serous | 30 (75) | 21 (81) | 9 (64) |
| Endometrioid | 2 (5) | 1 (4) | 1 (7) |
| Mucinous | 1 (2) | 1 (4) | 0 (0) |
| Clear cell | 7 (18) | 3 (12) | 4 (29) |

Number of treatment lines and treatment-duration are summarized in Table 2. Among all patients, median number of treatment lines was 3 (interquartile range (IQR) 1–6), and median number of platinum-containing lines was 2 (IQR 1–3). Among those who recurred, median number of treatment lines was 4 (IQR 3–6), and median number of platinum-containing lines was 2 (IQR 2–3). The decision to start a new line of chemotherapy was driven by disease recurrence or progression 83% of the time, whereas toxicity accounted for the remaining 17% of changes. On average, patients spent 20% (IQR 8–39%) of the time from diagnosis to death or date of last follow-up receiving cytotoxic chemotherapy, and 46% (IQR 14–65%) of the time on some form of cancer-directed therapy. For the subset of patients who recurred, the average amount of time spent receiving cytotoxic chemotherapy was higher at 32% (IQR 20–43%), and on any therapy it was 54% (IQR 41–67%).

Treatment modalities and chemotherapy agents utilized per treatment line are presented in Table 3. In the upfront setting, 15 patients (37%) received neoadjuvant chemotherapy, whereas 25 (62%) had a primary debulking surgery. Intraperitoneal chemotherapy was included in treatment line if the patient received any form of intraperitoneal chemotherapy until the date of death or last patient contact. The proportion of time on cytotoxic chemotherapy was calculated by adding each interval during which a patient received cytotoxic chemotherapy, and dividing this by the total amount of time elapsed from diagnosis to death or date of last contact. Similarly, the proportion of time spent on any cancer-directed therapy was calculated by adding each interval during which a patient had received any form of cancer-directed therapy and dividing this by the total amount of time. Cancer-directed therapy included any chemotherapy (neoadjuvant, adjuvant and maintenance), surgery and radiation, but excluded hospice and palliative-only care.

We calculated descriptive statistics as frequencies and proportions and compared characteristics between groups using t-tests for continuous data and chi-square tests or Fisher’s exact tests for categorical data. Survival times were calculated using the Kaplan-Meier method and differences in median survival between BRCA1 and BRCA2 mutation carriers were compared using the log-rank test. P-values < .05 were considered statistically significant. We created a Swimmer’s Plot to depict individual disease timelines.

| Table 2 | Number of treatment lines and treatment duration of patients with OC and germline BRCA mutations. In the first column, values are reported for all patients (n = 40), while in the second column values are presented for the subset of patients who recurred (n = 28). IQR = interquartile range. |
| --- | --- |
| Median (IQR) | All patients (n = 40) | Patients who recurred (n = 28) |
| Number of treatment lines | 3 (1–6) | 4 (3–6) |
| Number of platinum lines | 2 (1–3) | 2 (2–3) |
| Percent of time on cytotoxic chemotherapy | 20 (8–39) | 32 (20–43) |
| Percent of time on any chemotherapy | 46 (14–65) | 54 (41–67) |

* Includes all cytotoxic chemotherapy, bevacizumab, PARP inhibitors, other maintenance agents, and radiation.
given to 16 patients (40%). A maintenance regimen was given in 13 patients (32%) after completion of adjuvant treatment; 9 received bevacizumab, 1 carboplatin, 1 tamoxifen, and 2 experimental cancer therapy and half of their life on some form of cancer-directed therapy.

Our data describing successive lines of treatment are novel, given the scarcity of literature on the long-term treatment patterns of women with OC. A Dutch study by Houben et al. recently reported on the systemic treatments received by 261 patients with OC over multiple lines of therapy. They found that the median number of treatment lines was 2 (IQR 1–3) and identified 12 (5%) patients who received 8 or more lines. In keeping with our findings, they also noted significant variety in treatment patterns beyond second-line treatment (Houben et al., 2017). Our results provide additional details of treatment patterns, with an emphasis on treatment duration, and are the first to report specifically on patients with BRCA mutations.

Our estimates of overall survival correlate well to the published literature on BRCA-mutated OC, with prior estimates ranging from 53.4 to 100.8 months (Tan et al., 2008; Ben David et al., 2002; Chetrit et al., 2011). In spite of the generally favorable prognosis, it is interesting to note the range of responses seen in this cohort, with overall survival ranging from 14.8 to 139.2 months. While the small numbers available for this study precluded detecting significant differences in the characteristics of long-term responders and non-responders, our data challenge the notion that all BRCA-mutated carcinoma portends a better prognosis, and may reflect the presence of effect modification by other biological or treatment factors. For example, it would be interesting to consider if platinum non-responders have somatic reversions of the BRCA alleles to wildtype (Norquist et al., 2011). A strength of this study is that women with BRCA mutations were identified from a OC cohort enrolled at diagnosis in which all patients were tested for BRCA mutations, reducing genetic testing selection bias present in many studies of survival in BRCA-mutated OC.

This study has several limitations. It is a small, retrospective cohort of patients treated at a single institution, an academic center, where practice patterns may differ from community settings, thereby reducing generalizability. Additionally, our metrics of treatment duration (proportion of time spent on cytotoxic and on any cancer-directed therapy) is just one consideration when debating the merits of different treatment strategies, including maintenance therapy. Other factors, such as

### Table 3

| Neoadjuvant | 1st Line | 2nd Line | 3rd Line | 4th Line | 5th Line | 6th Line | 7th Line | 8th Line | 9th Line | 10th Line |
|-------------|----------|----------|----------|----------|----------|----------|----------|----------|----------|-----------|
| Chemotherapy | 15 (37) | 40 (100) | 26 (93) | 24 (86) | 18 (64) | 13 (46) | 11 (39) | 7 (25) | 7 (25) | 3 (11) |
| Cytoreduction | n/a | 40 (100) | 39 (119) | 2 (14) | 0 | 0 | 0 | 0 | 0 | 0 |
| Complete (≤1 cm) | n/a | 23 (57) | 7 (25) | 2 (7) | 0 | 0 | 0 | 0 | 0 | 0 |
| Suboptimal (>1 cm) | n/a | 13 (32) | 1 (4) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Intrapерitoneal route | 0 | 4 (10) | 3 (11) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Clinical trial | 0 | 2 (20) | 18 (89) | 7 (29) | 0 | 0 | 0 | 0 | 0 | 0 |
| Maintenance therapy | n/a | 13 (32) | 4 (14) | 1 (4) | 1 (4) | 0 | 0 | 1 (1) | 0 | 0 |
| Radiation | 0 | 0 | 1 (4) | 1 (4) | 0 | 1 (4) | 1 (4) | 1 (4) | 0 | 0 |
| Specific agents | (N = 15) | (N = 40) | (N = 26) | (N = 24) | (N = 18) | (N = 13) | (N = 11) | (N = 7) | (N = 7) | (N = 3) |
| Taxane | 14 (93) | 38 (95) | 4 (15) | 5 (21) | 5 (28) | 3 (23) | 2 (18) | 2 (29) | 1 (14) | 1 (33) |
| Liposomal doxorubicin | 0 | 0 | 6 (23) | 7 (29) | 2 (11) | 1 (8) | 2 (18) | 1 (14) | 0 | 0 |
| Gemcitabine | 1 (7) | 1 (3) | 10 (38) | 1 (4) | 3 (17) | 1 (8) | 1 (9) | 1 (14) | 1 (14) | 1 (33) |
| Topotecan | 0 | 0 | 1 (4) | 2 (8) | 2 (11) | 2 (15) | 0 | 1 (14) | 0 | 1 (33) |
| Bevacizumab | 0 | 0 | 5 (19) | 4 (17) | 4 (22) | 1 (8) | 1 (9) | 2 (29) | 1 (14) | 1 (33) |
| PARP inhibitor | 0 | 0 | 3 (12) | 2 (8) | 2 (11) | 2 (15) | 2 (18) | 0 | 1 (14) | 0 | 0 |

| Upfront treatment (n = 40) | Recurrence treatment (n = 28) |
|---------------------------|-----------------------------|

## Discussion

In this retrospective review, we investigated the disease courses of 40 BRCA mutation carriers with OC with long term follow up. Although BRCA-mutated OC is known to have high initial response rates to platinum therapy, we identified notable heterogeneity in secondary response and in overall disease course. Treatment duration was considerable, especially for women who recurred during the study period, who spent a third of their life after diagnosis receiving cytotoxic chemotherapy and half of their life on some form of cancer-directed therapy.
patient-reported quality of life, performance status, and rates of adverse events are clearly important. Nonetheless, even if a treatment is relatively well tolerated, it exacts substantial time and expense, and thus treatment duration remains relevant to patient-centered care. Given the paucity of detailed data on treatment-related burden for OC, these data represent a unique contribution, and may be particularly relevant for BRCA-mutated OC, where the availability of targeted maintenance regimens may further extend treatment durations.

Importantly, given the period of study (2004–2014), many patients did not receive PARP inhibitors. Current standard of care for BRCA-mutated recurrent OC is to use PARP inhibitors as stand-alone therapy or as maintenance therapy following response to platinum (Pujade-Lauraine et al., 2017), and PARP inhibitors will increasingly play a role as upfront maintenance therapy for BRCA carriers following the recent publication of the SOLO1 trial (Moore et al., 2018). As patients wrestle with the decision of whether to take on the toxicity of long-term PARP inhibitor following primary treatment, our data provide insight into the disease course in the absence of PARP inhibitor therapy. The large amount of time spent on active therapy and relatively low rate (15%) of 5-year disease free interval would argue favorably for the use of PARP inhibitor maintenance therapy in considering overall quality of life. It will be important to await data from the SOLO1 trial to assess whether the improvement in disease-progression at three years observed with olaparib maintenance after upfront treatment translates into durable responses and even cures. If this is the case, two years of maintenance PARP inhibitors may significantly reduce treatment duration in the long-run.

**Author contribution**

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Manuscript writing and editing: All authors.

Final approval: All authors.

Accountable for all aspects of work: All authors.
Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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