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Disease-free ovarian cancer patients report severe pain and fatigue over time: prospective quality of life assessment in a consecutive series

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Summary

Objective: Among ovarian cancer patients, cancer treatment is aggressive and yet survival is often so limited; hence, this study sought to measure quality of life with the ultimate goal of identifying ways of improving it over the duration of these patients' lives. *Materials and Methods:* The medical records of all ovarian cancer patients who received some/all of their initial chemotherapy at the Mayo Clinic in Rochester, Minnesota from late 2010 through 2012 were reviewed. Patient-reported quality of life was derived from the following ten-point linear analogue scale questions which had been administered to all patients: 1) How would you describe your degree of pain, on average? 2) How would you describe your level of fatigue, on average? 3) How would you describe your overall quality of life? Quality of life data were censored upon cancer recurrence. *Results:* Among 59 eligible patients, the median cumulative interval during which quality of life was serially assessed was 1.15 years (range: three months, 3.2 years). Area under the curve for pain, fatigue, and global quality of life showed no statistically significant differences between patients treated with dose-dense chemotherapy with carboplatin/paclitaxel (n=10) versus three-week chemotherapy with carboplatin/paclitaxel (n=36) versus other (n=13). Although pain, fatigue, and global quality of life improved over time, 35 of 59 (59%) patients reported grade 4 or worse pain during follow up, and 47 of 59 (80%) reported grade 4 or worse fatigue (higher scores denote worse pain or fatigue). After completion of cancer treatment, 30 (51%) described grade 4 or worse pain or fatigue. The most common pain site was the abdomen/pelvis, followed by the back, followed by the hands, feet, fingers, and toes. *Conclusion:* In ovarian cancer patients who remain cancer-free, severe pain and fatigue occur years after cancer treatment. Further research should focus on how best to address these symptoms.

Key words: Pain; Fatigue; Quality of life; Ovarian cancer.

Introduction

Over 70% of ovarian cancer patients are diagnosed with late-stage disease, undergo an extensive lymphadenectomy and an omentectomy in conjunction with extirpation of multiple pelvic organs, and then go on to receive further cancer treatment in the form of several cycles of chemotherapy — only to die, oftentimes within five years, of recurrent cancer [1]. This sobering pattern of events has prompted contemporary, large-scale therapeutic trials in ovarian cancer patients to integrate quality of life measurements into their study design: if cancer treatment is so aggressive and survival often so limited, it seems appropriate to measure quality of life with the ultimate goal of improving it over the duration of these patients' short lives.

These large-scale clinical trials have provided salient observations on quality of life. First, in ovarian cancer patients receiving potentially curative therapy, symptoms appear to diminish as cancer treatment continues. For example, in a phase III trial that assessed the role of neoadjuvant chemotherapy for the treatment of ovarian cancer, Greimel *et al.* observed that, among 404 patients, cancer symptoms such as pain and fatigue decreased over time [2]. Second, maintenance therapy confers a negative impact on quality of life. Monk *et al.* examined quality of life among 1,693 ovarian cancer patients who participated in Gynecological Oncology Group Study 0218 and found that patients who received maintenance bevacizumab manifested an approximately 10% decline in global quality of life over time [3]. Similar results were reported in the quality of life assessment from the ICON7 trial, which also tested maintenance bevacizumab [4]. Finally, quality of life in the Gynecological Oncology Group Study 0172 showed that intraperitoneal chemotherapy leads to "more health-related quality-of-life disruption," specifically more abdominal pain and peripheral neuropathy, compared to a more typically-administered intravenous chemotherapy regimen [5]. Thus, quality of life assessment has become an important part of prospectively-conducted clinical trials and serves an important role in the assessment of new cancer treatments.

Nonetheless, gaps exist. First, weekly, dose-dense chemotherapy with carboplatin and paclitaxel has gained notable recognition based on its conferred survival advan-

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tage over three-week chemotherapy, as reported in the Japanese Gynecological Oncology Group 3016 study [6, 7]. To the present authors' knowledge, however, few previous studies have examined whether dose-dense chemotherapy is associated with a comparative change in global quality of life. Second, although quality of life assessment is increasingly integrated into prospectively-conducted clinical trials, only a relatively small number have focused on long-term quality of life in patients who are not enrolled in a clinical trial [8-20]. This distinction between whether or not patients had enrolled in a trial is not trivial, as the latter group often has a more advanced age, an inferior performance score, a greater number of co-morbid conditions and, hence, not surprisingly, a greater number of severe treatment-related adverse events [21, 22].

In view of the foregoing, the purpose of the current study was twofold. First, the authors sought to explore quality of life differences between patients who received dose-dense chemotherapy as part of their initial cancer treatment versus other patient groups. To their knowledge, these data may be among the first to examine comparative quality of life with this regimen. Second, the authors sought to describe prospectively derived quality of life data from a more typical group of ovarian cancer patients, the majority of whom had not been enrolled in a clinical trial. Because over 90% of ovarian cancer patients are not enrolled in clinical trials, such descriptive data would be invaluable to understand what most ovarian cancer patients are experiencing [22].

Materials and Methods

Overview

The Mayo Clinic Institutional Review Board approved this study. A study nurse, who was affiliated with the Mayo Clinic Ovarian Specialized Program of Research Excellence (SPORE) grant and routinely recorded the names of all patients treated for ovarian cancer at the Mayo Clinic in Rochester, Minnesota, provided a list of patients from late 2010 through 2012. This starting date was chosen because the Japanese Gynecological Oncology Group Study 3016 with dose dense chemotherapy was published shortly prior and because the Mayo Clinic Medical Oncology Clinic began prospectively to capture and record quality of life data in late 2010 [7]. Patients were deemed eligible for inclusion in the current study if they had a diagnosis of ovarian cancer and had received their initial peri-operative chemotherapy at the Mayo Clinic in Rochester, Minnesota.

Data Acquisition

All records were reviewed in depth by two investigators (SS and TW) with spot checks for accuracy by another (AJ). Extracted data included patients' date of birth, vital status at time of medical record review, date of death or last follow up, cancer stage and histology, date of surgery, dates of chemotherapy, type of chemotherapy initially administered (weekly, dose dense carboplatin/paclitaxel versus three-week carboplatin/paclitaxel versus other), number of completed cycles, and whether recurrent cancer had been diagnosed, and, if so, when. If a patient needed to switch to a different regimen, such information was also recorded.

Table 1. — *Baseline and treatment demographics.*

	Dose-dense chemotherapy N=10	3-week chemotherapy N=36	Other N=13
Age,* median (range)	55 (30, 73)	63 (36, 85)	60 (40, 87)
Cancer Stage**			
1	3 (30)	9 (25)	1 (8)
2	0	3 (8)	2 (16)
3	7 (70)	18 (50)	9 (69)
4	0	5 (14)	1 (8)
Tumor histology			
Serous	7 (70)	25 (69)	8 (61)
Endometrioid	1 (10)	4 (10)	1 (8)
Other	2 (20)	7 (19)	4 (31)
Neoadjuvant chemotherapy? Yes	0	4 (10)***	1 (8)
Median number of chemotherapy cycles (range)****	6 (3,6)	6 (3,8)	6 (4,6)
Switched chemotherapy? Yes	1 (10)	2 (6)	1 (23)
Recurrent cancer? Yes	5 (50)	16 (44)	5 (38)

* denotes age at start of chemotherapy;
** numbers may not sum to 100% because of rounding and numbers in parentheses denote percentages unless otherwise specified;
*** one patient who received 3-week chemotherapy did not undergo surgery;
**** if maintenance non-cytotoxic agents were used per a clinical trial, these agents were not counted in the cycle.

Quality of life information

Patient-reported quality of life was extracted from each medical record along with the date the patient completed the previousvalidated questionnaire items [23]. This patient-reported information was derived from the following three questions: 1) How would you describe your degree of pain, on average? 2) How would you describe your level of fatigue, on average? 3) How would you describe your overall quality of life? Patients were asked to "check only one" option on a scale from 0-10 that used verbal descriptions on the ends of the scale to denote the severity of each specific symptom or condition. These quality of life questions and responses were administered with paper and were provided to each patient at each visit if it occurred within two weeks or longer of the previous visit; clinic staff recorded patients' questionnaire responses in the medical record.

If a patient had graded her pain as a 4 or worse, as per the patient-reported pain question described above, that patient's medical record from the date of the severe pain was re-reviewed to learn the source of pain. This pain score threshold was chosen because it has precedent for denoting clinically significant, severe pain [24]. Starting at the time of recurrent disease, quality of life data were censored to avoid the confounding negative effect of recurrent cancer.

Data analyses

Data are presented descriptively with means, medians, standard deviations, ranges, percentages, and graphics, as appropriate. For the primary analysis of quality of life based on type of peri-operative chemotherapy, area under the curve (AUC) was calculated for each of the three patient-reported quality of life questions over time [25]. These AUC values were based on the time from first chemotherapy until last-reported quality of life score. To adjust for differences in patient follow-up, the AUC was then divided by the time from chemotherapy to last reported value. Analysis of vari-

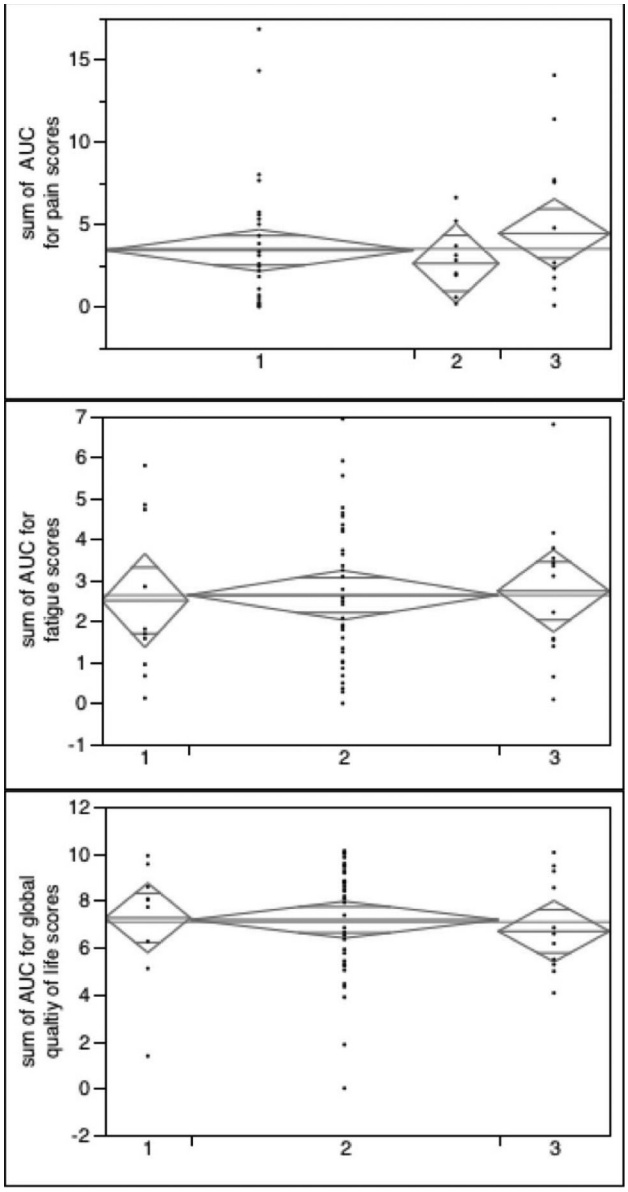

Figure 1. — Comparisons of area under the curve for pain, fatigue, and global quality of life scores showed no statistically significant differences between patients treated with dose-dense chemotherapy (1) versus three-week chemotherapy (2) versus other (3). Boxplots show 95% confidence intervals.

ance was used to compare area under the curve between the three treatment groups. JMP, version 9 was used for all analyses. All tests were two-sided, and p-values of < 0.05 were judged statistically significant.

Results

Demographics and treatment summary

Fifty-nine ovarian cancer patients met the study eligibility criteria. Baseline and treatment demographics appear in Table 1.

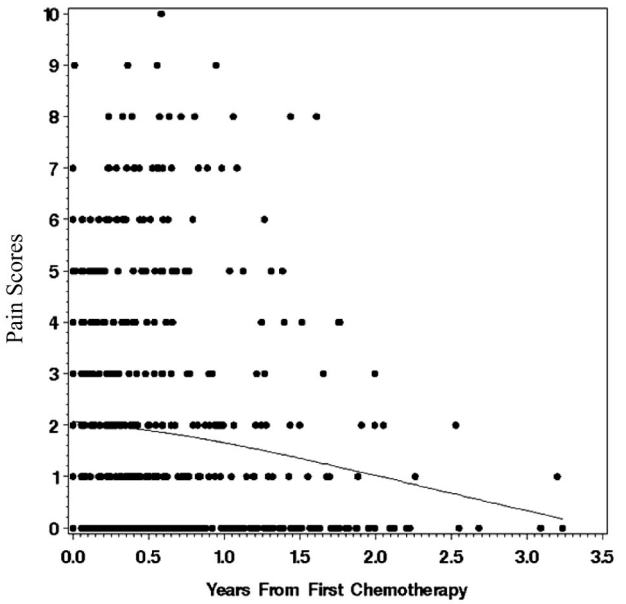

Figure 2. — Thirty-five of 59 patients reported grade 4 or worse pain (higher scores denote worse pain) at some point during follow-up. Each dot represents a pain score and the inserted line shows the trend.

Ten patients received weekly, dose-dense chemotherapy with carboplatin and paclitaxel; 36 received three-week chemotherapy with these same agents; and 13 received another chemotherapy regimen, termed "other." Nine patients had been enrolled in a chemotherapy treatment trial and were included in this other category. Five patients received neoadjuvant chemotherapy, and only four needed to switch to another regimen. All but one underwent surgery, and this patient had received three-week chemotherapy. At the time of this report, 26 patients had developed recurrent cancer, and six had already died.

Quality of life assessment

Patients completed an assessment of pain, fatigue, and global quality of life at one time point or more. The number of quality of life assessments per patient ranged from 1 to 20 over time. Although the frequency of assessment varied widely even intra-patiently, the median cumulative interval during which quality of life was serially assessed was 1.15 years (range: three months, 3.2 years).

Comparisons of AUC for pain, fatigue, and global quality of life scores showed no statistically significant differences between patients treated with dose-dense chemotherapy versus three-week chemotherapy versus other (Figure 1). For pain, AUC (standard deviation) was 2.6 units/year (2.1) versus 3.4 units/year (3.9) versus 4.6 units/year (4.4), for patients who had received dose-dense, three-week, and other chemotherapy, respectively (p = 0.51). For fatigue, 2.5 units/year (2.0) versus 2.6 units/year (1.8) versus 2.7

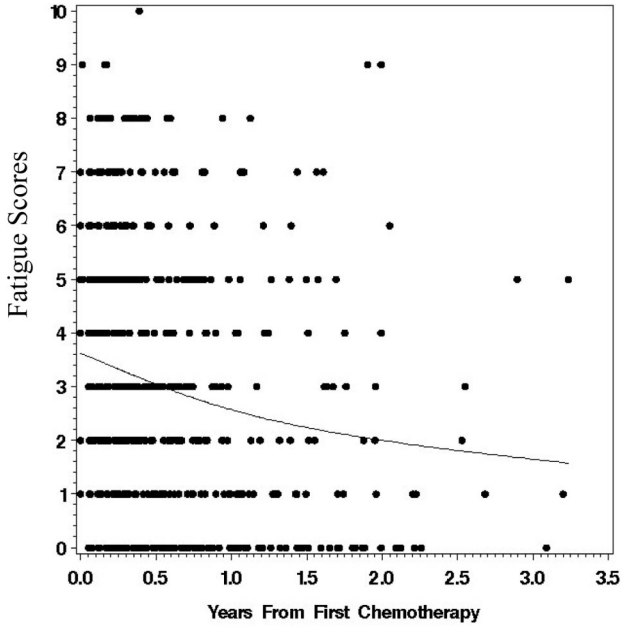

Figure 3. — Forty-seven of 59 patients reported grade 4 of worse fatigue (higher scores denote worse fatigue) at some point during follow-up. Each dot represents a fatigue score and the inserted line shows the trend.

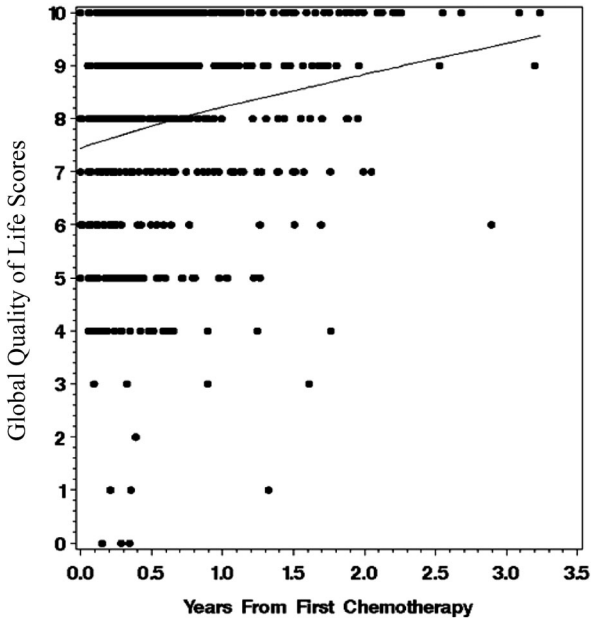

Figure 4. — Seventeen of 59 patients reported grade 4 or worse general quality of life at some time point (lower scores denote worse quality of life) at some point during follow-up. Each dot represents a global quality of life score, and the inserted line shows the trend.

units/year (1.8) was observed for patients who received dose-dense, three-week, and other chemotherapy, respectively; $p = 0.95$. Finally, for global quality of life, 7.3 units/year (2.5) versus 7.2 units/year (2.4) versus 6.7 units/year (2.0) was observed for patients who received dose-dense, three-week, and other chemotherapy, respectively ($p = 0.78$).

Descriptive quality of life data

Trends suggest that pain, fatigue, and global quality of life improved over time (Figures 2-4). However, 35 of 59 (59%) patients reported grade 4 or worse pain at some point during follow up, and 47 of 59 (80%) reported grade 4 or worse fatigue (higher scores denote worse pain or fatigue). Of note, after completion of cancer treatment, 30 patients (51%) described grade 4 or worse pain or fatigue. Seventeen (29%) described grade 4 or worse general quality of life at some time point (lower scores denote worse quality of life) (Figures 2-4).

The most common site of pain was in the abdomen/pelvis and was cited 37 times in the medical records within the cohort. This site was followed by back pain, which was cited 20 times. Pain in the hands, feet, fingers, and toes was cited 20 times.

Discussion

This study first sought to explore whether quality of life over time was markedly different in patients treated with dose-dense chemotherapy with paclitaxel and carboplatin, as per the Japanese Gynecological Oncology Group 3016, versus three-week chemotherapy versus some "other" regimen. Secondly, it sought to provide serial, prospective, descriptive data on patient-reported quality of life in a group of patients, the majority of whom had received care outside a cancer therapeutics trial. With regards to this first goal, this study found no glaring differences in quality of life between treatment groups. These findings suggest that current practice when prescribing dose-dense chemotherapy should not be modified but that further study of quality of life with dose-dense chemotherapy in ovarian cancer patients is warranted.

Importantly, this study's secondary goal uncovered the most noteworthy observations. Similar to other studies, this study observed trends of symptom improvement over time [2]. However, trends do not always tell the whole story. For some patients within this cohort, severe pain and fatigue persisted for years after completion of initial cancer therapy and occurred in the absence of recurrent cancer. Indeed, the observation that 30 of 59 patients suffered grade 4 or worse pain and/or fatigue after completion of cancer treatment underscores the fact that, as a cohort, ovarian cancer patients have major unmet needs that persist over time. Furthermore, the fact that most of these patients will likely die from recurrent cancer in the near future only further points to the urgency of working to address these needs.

How does this study differ from other quality of life studies in ovarian cancer patients? First, in contrast to

many previous studies, the authors of this report provided more than averages and trends when we reported on quality of life. Indeed, a recent review from Lorusso *et al.* advocates for moving beyond reporting trends in global quality of life assessment [26]. By identifying large subgroups of patients who had severe pain and fatigue, the current study is in keeping with this recommended approach. Second, this study's retrospective design, which included a prospective evaluation of quality of life in all patients as part of routine clinical care, is another major strength. As a result of this study design, the present results are not biased from patient selection. Third, in the current study, the authors distinguished between patients who were cancer-free and those who had developed recurrent cancer, censoring the latter. To their knowledge, relatively few quality of life studies have scrutinized patients' health status to the point of being able to make this distinction. This distinction is important because it shifts the emphasis away from cancer therapy towards treating the patient for the residual effects of surgery and chemotherapy, a focus that has perhaps received less attention in the past. Finally, the current study focused on pain in contrast to some earlier studies that focused only on global quality of life. Acknowledged as the fifth vital sign, pain is often highly treatable yet often ignored [27]. The present observation that this highly treatable symptom is severe and prevalent in long-term ovarian cancer survivors can potentially foster changes in clinical practice and hence relieve suffering for patients with ovarian cancer.

This study has both limitations and strengths that revolve primarily around its limited sample size. Because only a small number of patients had received dose-dense chemotherapy, some of our preliminary conclusions on comparative quality of life with dose-dense chemotherapy must be viewed with caution. However, this relatively smaller sample size is also a strength. It allowed the authors to examine long-term quality of life data in much greater detail, to identify subgroups of patients who suffer from severe pain and fatigue long-term, and to even report on the physical location of that pain. As a result, we are able to clearly articulate this study's most salient finding that severe pain and fatigue occurs many months/years after cancer treatment in ovarian cancer patients who remain cancer-free and that further research should focus on how best to address these symptoms.

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