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Case series

Aspirin use correlates with survival in women with clear cell ovarian cancer

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ABSTRACT

Data from colon, breast and prostate cancers suggest that aspirin users have reduced mortality. While the direct mechanism remains uncertain, aspirin can suppress the COX-dependent and independent pathways involved in tumor progression. We hypothesized that aspirin users with clear cell ovarian cancer would have improved survival outcomes.

We performed a retrospective review of patients with clear cell ovarian cancer diagnosed between 1995 and 2010, and followed outcomes through 2016. Patients underwent primary cytoreductive surgery followed by platinum-based chemotherapy. Aspirin use was defined by medication documentation in two records more than six months apart. Statistical tests included Fisher's exact, Kaplan-Meier and Cox regression analyses.

Seventy-seven patients met inclusion criteria. Fifty-four patients (70%) had stage I-II disease. Thirteen patients (17%) used aspirin. Aspirin users had a statistically longer disease-free survival compared to non-users (HR 0.13, $p = .018$). While median disease-free survival was not reached for either group, 1 of 13 (8%) aspirin users recurred at 24 months, compared to 18 of 64 (28%) non-users. Aspirin users demonstrated longer overall survival (HR 0.13, $p = .015$). Median survival was not reached for aspirin users, compared to 166 months for non-users. Aspirin use retained significance (HR 0.13, $p = .044$) after controlling for age, stage and cytoreductive status.

In this small cohort of women with clear cell ovarian cancer, aspirin use correlated with improved disease-free and overall survival, and retained independent significance as a positive prognostic factor. Further research is warranted to confirm these findings before considering aspirin as a therapeutic intervention.

1. Introduction

Clear cell ovarian cancers represent approximately 5–10% of epithelial ovarian cancers, and often arise from endometriosis. Although typically diagnosed at an early stage, patients with stage III and IV clear cell ovarian cancer show poor response to standard platinum-taxane chemotherapy regimens and have a higher risk of disease recurrence (Anglesio et al., 2011; Chan et al., 2008). Additionally, thromboembolic events occur more frequently in patients with clear cell ovarian cancer contributing to increased morbidity and mortality (Anglesio et al., 2011; Diaz et al., 2013).

It is well supported that aspirin, and other non-steroidal anti-inflammatory medications, may have a role in the prevention of malignancy (Burn et al., 2011; Algra and Rothwell, 2012). However in recent years, there has been growing interest in incorporating aspirin into the multimodal treatment of various malignancies (Langley et al., 2011; Elwood et al., 2016). Research suggests that aspirin influences numerous biologic mechanisms known to be involved in tumor progression, including suppression of COX-dependent and COX-independent pathways. In particular, inhibition of COX-dependent pathways reduces inflammation and may impede tumor growth, angiogenesis, invasion and metastasis (Langley et al., 2011). Furthermore, in vitro studies suggest that interactions between platelets and ovarian cancer cells can result in increased tumor cell invasion, thus revealing another mechanism by which aspirin may be effective as a therapeutic agent (Cooke et al., 2015).

In 2016, a systematic review and meta-analysis assessing the impact of aspirin use following a cancer diagnosis showed improved mortality outcomes in breast, prostate, and most notably, colon cancer (Elwood et al., 2016). Furthermore, an enhanced reduction in mortality was noted in colorectal tumors expressing PIK3CA mutations compared to wild type tumors (Elwood et al., 2016; Liao et al., 2012). The PIK3CA gene encodes a cell membrane protein kinase involved in cell growth, proliferation, differentiation and survival. Tumors with PIK3CA gene mutations are known to have heightened activity of the COX-2 pathway and subsequently more prostaglandin release, potentially explaining the documented augmented response to aspirin therapy (Elwood et al., 2016). Interestingly, PIK3CA mutations occur in 20–30% of clear cell

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ovarian cancers, compared to < 1% of high-grade serous epithelial ovarian tumors (Campbell et al., 2004; Kuo et al., 2009). This leaves a unique opportunity to evaluate the impact of aspirin on the clinical outcomes of patients with clear cell ovarian cancer.

We hypothesized that aspirin use would correlate with improved survival outcomes for women with clear cell ovarian cancer. We aimed to identify aspirin users within a cohort of women with clear cell ovarian cancer at a single institution, and to detect potential relationships with clinico-pathologic prognostic factors and patient survival outcomes.

2. Methods

The Gynecologic Oncology service at Cedars-Sinai Medical Center maintains a prospective database of all patients diagnosed with gynecologic malignancies. After obtaining IRB approval, the database was queried and all patients diagnosed with clear cell ovarian cancer from 1995 to 2010 were identified, and outcomes were followed through 2016. Patients were included in this study if they underwent standard of care therapy via primary cytoreductive surgery with the intention of complete surgical resection of disease, followed by at least six cycles of platinum-based chemotherapy. Patients with low-grade histology or who underwent neoadjuvant chemotherapy were excluded.

Optimal cytoreductive surgery was defined as residual disease of < 1 cm. Patients with subsequent recurrent disease were treated with surgery and/or chemotherapy at the discretion of the treating physician. Medical records for all eligible patients were reviewed and data was abstracted including aspirin use, clinico-pathologic factors, and time to disease recurrence and death. Patients were considered aspirin users if either 81 mg or 325 mg of the medication was documented in at least two distinct medical records greater than six months apart. Data was analyzed using Fisher's exact test, Kaplan-Meier survival, and Cox regression analyses. A p-value of < 0.05 was considered statistically significant.

3. Results

Seventy-seven patients met criteria for inclusion. The average age of the cohort was 53 years (range 24–88). The majority of the cohort (81%) identified as White, and 17% as Asian. Forty-three patients (56%) had stage I, 11 (14%) had stage II, 19 (25%) had stage III, and 4 (5%) had stage IV disease. All patients had high-grade disease. Forty-two patients (55%) were noted to have endometriosis identified on pathology report (Table 1). Thirteen patients (17%) were considered aspirin users. Reasons for aspirin use included cardiovascular protection and symptom management. For purposes of comparison, we divided the cohort into aspirin users (n = 13) and aspirin non-users (n = 64) (Table 1). There was a significantly larger proportion of aspirin users with stage I disease compared to aspirin non-users (85% versus 50% respectively, p = .02). The proportion of stage II-IV disease was evenly matched between aspirin users and non-users. Within the entire cohort, 73 patients (95%) underwent optimal cytoreductive surgery at initial exploration with equal distribution among groups (p = .37). Further analysis of the 23 patients with stage III-IV disease showed a similar optimal cytoreduction rate of 87%. There were no hemorrhagic complications documented in the medical record. Venous thromboembolism, diagnosed post-operatively or at the time of disease recurrence, occurred in 11 patients (14%), and the incidence was equally distributed between groups (p = .92).

To evaluate the influence of aspirin use on disease progression and patient overall survival we performed Kaplan-Meier survival analyses. Aspirin users had statistically longer disease-free survival compared to non-users (HR 0.13, 95% CI 0.13–0.83, p = .018) (Fig. 1). In this cohort of patients, median disease-free survival was not reached for either group. However, 1 in 13 aspirin users (8%) recurred at 24 months, compared to 18 of 64 aspirin non-users (28%). The one aspirin user who recurred by 24 months had stage IC disease; of the 18 recurrent aspirin non-users, 5 (28%) had stage I, 1 (6%) had stage II, 10 (56%) had stage III, and 2 (11%) had stage IV disease. Additionally, aspirin users demonstrated longer overall survival (HR 0.13, 95% CI 0.13–0.81, p = .015) (Fig. 2). Median overall survival was not yet reached for aspirin users, whereas median survival was 166 months for non-users.

In order to determine the independent prognostic impact of aspirin in this cohort, multivariate COX regression analyses were conducted (Table 2). After controlling for established prognostic factors in clear cell ovarian cancer including age, stage and cytoreductive status, aspirin use retained independent significance as a positive prognostic factor (HR 0.13, 95% CI 0.017–0.947, p = .044). Additionally, disease stage was a statistically significant independent negative prognostic factor (HR 1.62, CI 1.027–2.545, p = .038). There was no significant association between patient age (HR 1.03, CI 1.002–1.051, p = .038) or suboptimal tumor cytoreduction (HR 4.37, CI 0.490–38.991, p = .187) and prognosis.

Table 1
Cohort characteristics and distribution of clinico-pathologic prognosticators between aspirin users and aspirin non-users.

Variable	Cohort (n = 77)	Aspirin users (n = 13)	Aspirin non-users (n = 64)	p-Value
Mean age at diagnosis (years)	53.4 ± 13.8	57.9 ± 13.0	52.3 ± 13.9	0.19
Race				
White	62 (80.5%)	12 (92%)	50 (78%)	0.25
Asian	13 (17%)	1 (8%)	12 (19%)	0.34
American Indian/ Alaska Native	2 (2.5%)	0 (0%)	2 (3%)	0.53
African American	0 (0%)	0 (0%)	0 (0%)	–
Stage				
I	43 (56%)	11 (85%)	32 (50%)	0.02
II	11 (14%)	0 (0%)	11 (17%)	0.11
III	19 (25%)	2 (15%)	17 (27%)	0.37
IV	4 (5%)	0 (0%)	4 (6%)	0.37
Grade				
2	2 (2.5%)	0 (0%)	2 (3%)	0.53
3	75 (97%)	13 (100%)	62 (97%)	0.54
Optimal cytoreduction	73 (95%)	13 (100%)	60 (94%)	0.37
Endometriosis	42 (55%)	7 (54%)	35 (55%)	0.95
Hemorrhagic complications	0 (0%)	0 (0%)	0 (0%)	–
Post-operative thromboembolism	11 (14%)	2 (15%)	9 (14%)	0.93

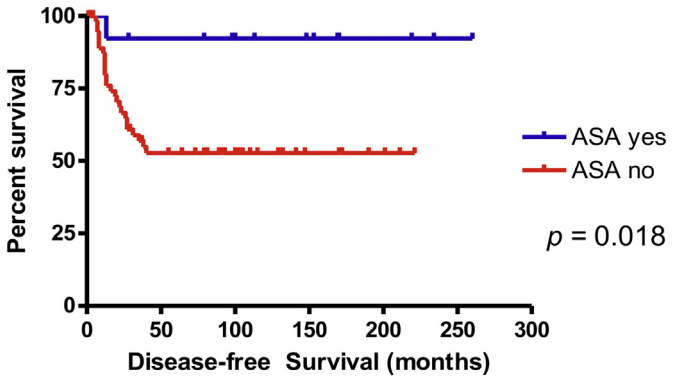

Fig. 1. Effect of aspirin on disease-free survival. Aspirin users had a statistically greater disease-free survival compared to non-users. Median disease free survival was not reached for either group. However, 8% of aspirin users recurred at 24 months, compared to 28% of aspirin non-users.

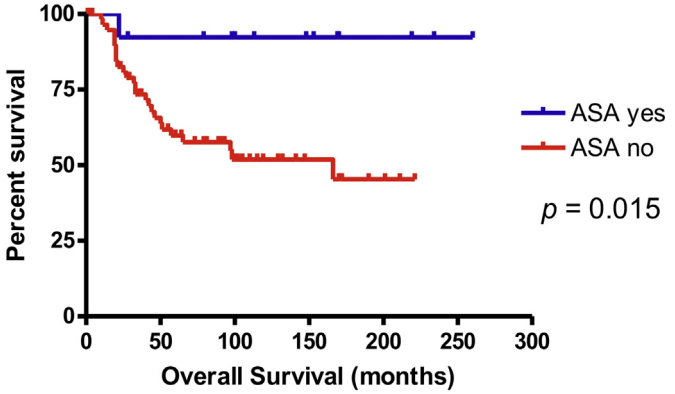

Fig. 2. Effect of aspirin on overall survival. Aspirin users demonstrated improved overall survival. Median overall survival was not yet reached for aspirin users, whereas median survival was 166 months for non-users.

Table 2
Multivariate Cox proportional hazard analysis of potential prognostic factors on survival. Aspirin use reduced the chance of death by 87% compared with that of non-users.

Variable	Hazard ratio	95% confidence interval	*p*-Value
Age	1.03	1.002–1.051	0.038
Stage	1.62	1.027–2.545	0.038
Suboptimal cytoreduction	4.37	0.490–38.991	0.187
Aspirin use	0.13	0.017–0.950	0.044

4. Discussion

We hypothesized that aspirin use may influence clear cell ovarian cancer biology through alterations in both the COX-dependent and COX-independent pathways, leading to improved patient survival outcomes. In this cohort of patients with clear cell ovarian cancer, we did identify a statistically significant association between aspirin use and both disease-free and overall survival. We observed that aspirin use retained significance as an independent prognostic factor even when controlling for confounding variables such as age, stage, and cytoreductive status. Additionally, the incidence of post-diagnostic thromboembolism was similar between aspirin users and non-users, indicating that the observed improvement in survival is not likely attributed to prevention or treatment of non-cancer specific causes of death such as deep venous thrombosis and pulmonary embolism. In our cohort, aspirin use was found to be safe, with no hemorrhagic complications identified.

To date, there remains a paucity of research evaluating the influence of aspirin on survival for those with ovarian cancer, and the results are complex and conflicting. In recent years, two studies have evaluated survival outcomes for patient's using aspirin prior to their diagnosis of invasive epithelial ovarian cancer (Minlikeeva et al., 2015; Dixon et al., 2017). Minlikeeva et al. (2015) in a 5-year case-control study of 699 women with epithelial ovarian cancer found no association between low or high dose aspirin use and survival. Dixon et al. (2017) performed a pooled analysis of 7694 women within 12 case-control studies of patient-reported pre-diagnostic NSAID use in invasive epithelial ovarian cancer. They similarly found no significant improvement in either progression-free or overall survival when analyzing aspirin users alone. Furthermore, several studies have evaluated survival outcomes in patients with post-diagnostic aspirin use, again with mixed results (Bar et al., 2016; Verdoodt et al., 2018). Bar et al. (2016) in a retrospective cohort study of 143 patients with ovarian cancer, analyzed aspirin use in the context of metabolic syndrome and the subsequent impact on survival. Results indicated a statistically significant improvement in disease-free and overall survival for those taking aspirin after their cancer diagnosis. This contradicted findings by Verdoodt et al. (2018) in a large retrospective cohort study of 4117 patients within the Danish Cancer Registry that found no association between post-diagnostic aspirin use and survival in patients with epithelial ovarian cancer, despite separately analyzing the various histologic subtypes.

The conflicting conclusions of the aforementioned studies may be a result of inconsistent definitions of “aspirin use”, including timing, dosage, frequency, or duration of use. Additionally, as suggested by previous data, one could postulate that longstanding pre-diagnostic use of aspirin could result in a state of “tumor resistance”, such that no significant survival impact would be obtained outside of novel users (Elwood et al., 2016). Data collected in our study incorporated patients with both pre-diagnostic and post-diagnostic use of aspirin, and due to constraints of retrospective chart review could not be analyzed separately. Lastly, the histologic subtypes of epithelial ovarian cancer are known to arise from different pathogenic processes. Clear cell ovarian cancer often originates from endometriosis, an inflammatory driven process, which could have contributed to the observed survival benefit for aspirin users in our study (Anglesio et al., 2011).

Although conclusions regarding the impact of aspirin use in ovarian cancer are mixed, our findings are strongly supported by colon cancer literature. Research suggests that aspirin down regulates COX inflammatory pathways, particularly in patients with activating PIK3CA mutations, to ultimately affect multiple mechanisms involved in tumor progression and metastasis (Langley et al., 2011; Elwood et al., 2016; Liao et al., 2012). PIK3CA mutations are equally, if not more, prevalent in clear cell ovarian cancer as compared to colon cancer (Campbell et al., 2004; Kuo et al., 2009). Therefore, future studies should investigate if women with clear cell ovarian cancer and PIK3CA mutations demonstrate an enhanced survival response to aspirin therapy.

Our study is inherently limited by its retrospective design, which permits only correlative conclusions, and the challenges of chart review. Additionally, we are limited by the small cohort size of 77 patients, of which only 17% met criteria for aspirin use. Given that clear cell ovarian cancer is often diagnosed in middle age, before the onset of medical conditions that would warrant chronic aspirin use, this may be a logical and expected proportion of medication use in this cohort. Analysis of our patient characteristics also revealed that a larger proportion of aspirin users were diagnosed with stage I disease when compared to non-aspirin users; other clinic-pathologic prognostic factors such as patient age, optimal cytoreduction and stage II-IV disease were evenly distributed between groups. Although this is a potential confounder in our study, the discrepancy can likely be attributed to the small sample of aspirin users and the predominance of early stage disease in clear cell ovarian cancer. When adjusted for in the multivariate analysis, aspirin use retained statistical significance as an independent positive prognostic factor, thus supporting the potential therapeutic utility of aspirin. Additionally, because the majority of this cohort had stage I-II disease, we expect that a longer follow-up period will be necessary to approach median survival for both aspirin users and non-users. However, it is compelling that a significantly higher proportion of aspirin users were alive at each follow up point as exhibited in the Kaplan-Meier plots.

Although the exact mechanism by which aspirin contributes to improved survival outcomes in both gynecologic and other cancer types remains under investigation, our data support that further study is warranted. In both in vitro and in vivo models, aspirin has been shown to influence carcinogenesis leading to clinically relevant improvements in survival. Moreover, aspirin is an affordable and readily available medication, and in properly selected patients carries an acceptable risk with regards to hemorrhagic and gastrointestinal complications. As we continue to evaluate the use of multimodal cancer therapies, it is imperative to consider the broader role of aspirin in altering tumor biology.

Conflict of interest statement

The authors have no relevant financial relationships or conflicts of interest to report.

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