Gynecologic Oncology Reports 25 (2018) 78–81

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case series

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

Alyssa M. Wield*, Christine S. Walsh, B.J. Rimel, Ilana Cass, Beth Y. Karlan, Andrew J. Li

Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Cedars-Sinai Medical Center, Los Angeles, CA, USA

ARTICLE INFO

Keywords:
Clear cell
Ovarian cancer
Aspirin
Survival
PIK3CA

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

* Corresponding author at: Cedars-Sinai Medical Center, 8700 Beverly Blvd, Suite 3622, Los Angeles, CA 90048, USA.
E-mail address: Alyssa.Wield@cshs.org (A.M. Wield).

https://doi.org/10.1016/j.gore.2018.06.004
Received 20 April 2018; Received in revised form 7 June 2018; Accepted 8 June 2018
Available online 09 June 2018

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

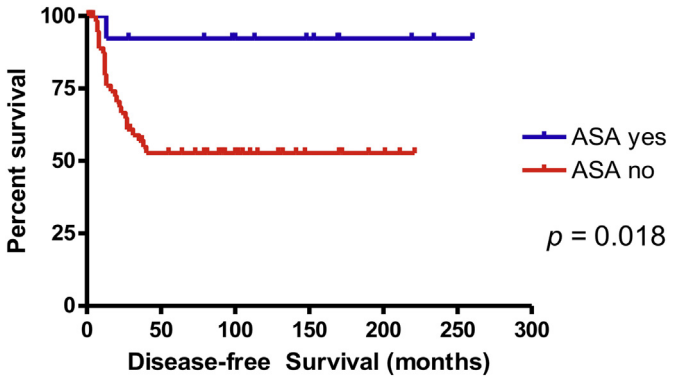

Fig. 1. Effect of aspirin on disease-free survival. Aspirin users had a statistically greater disease-free survival compared to non-users. Median disease free survival was not reached for either group. However, 8% of aspirin users recurred at 24 months, compared to 28% of aspirin non-users.