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Statin Use is Associated with Increased Survival in Patients with Advanced Epithelial Ovarian Cancer: Institutional Experience and Literature Review

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Abstract

Introduction and objective: Statin use have been associated to better outcomes in cancer survival, specifically ovarian cancer. The objective of this article is to determine the association between statin consumption and increased Disease-Free Survival (DFS) as well as Overall Survival (OS) in patients with Epithelial Ovarian Cancer (EOC).

Methods: We performed a retrospective analysis of patients with diagnosis of EOC at any stage, who underwent treatment with cytoreductive surgery and neoadjuvant or adjuvant chemotheraphy. Demographic, clinical and laboratory data was recollected, as well as the use of statins at diagnosis or during treatment, DFS and OS.

Results: One hundred and twenty-one patients were included. Thirteen (10.7 %) consumed statins at diagnosis and during follow-up. Median age was 53.7 years. Stage distribution was 21% stage I, 2.5% stage II, 55.5% stage III and 21% stage IV. Optimal cytoreduction was obtained in 68% of patients. In the subgroup analysis of patients with stage IIIC, median DFS was 40.6 months for statin users and 11.5 months for non-users (p=0.000), while OS was 81.2 vs 36.8 months respectively (p=0.065).

Conclusions: Statin use is associated with increased survival in patients with stage IIIC EOC.

Keywords: Ovarian cancer; Statins; Survival.

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Introduction

Epithelial Ovarian Cancer (EOC) is the deadliest gynecological cancer, representing the fourth most common cause of cancer related death among women worldwide [1]. The lifetime probability of developing EOC for women living in the United States is estimated between 1.4 and 1.8% [2].

Statins inhibit hydroxymethylglutarate Coenzime-A reductase (HMGCR), reducing plasma cholesterol and therefore used as treatment for dyslipidemia. They have shown to reduce morbidity and mortality in cardiovascular disease [3,4]. Besides that, statins have shown to inhibit tumor growth, angiogenesis and metastasis [5]. They also reduce inflammatory response and smooth-muscle proliferation, thus improving endothelial function. These effects are due to the inhibition of isoprenoids, intermediate products of cholesterol synthesis, but independent of cholesterol serum concentration [6]. Therefore, statins exert pleiotropic effects, independent of its effect over cholesterol [7].

This evidence suggests that statins might be useful as adjuvant treatment for certain types of cancer through its interactions with key cellular functions, such as proliferation and differentiation. The objective of this article is to describe the association between statin use and survival in patients with diagnosis of EOC.

Patients and methods

We performed a retrospective search for patients diagnosed with epithelial ovarian cancer at a tertiary level care center in Mexico City. We included patients with EOC who underwent cytoreductive surgery and received neoadjuvant or adjuvant chemotherapy. The timing for chemotherapy and surgery was decided in and individualized manner in a multidisciplinary surgical oncology meeting with and expert panel. Cytoreductive surgery was performed by two surgical oncologists at out institution, and the extent of the resection was decided intraoperatively depending on the findings. Optimal cytoreduction was defined by and R0-R1 resection, meaning no gross residual disease was observed. All patients that were being treated with statins were identified. Patients with any other histologic type than EOC as well as patients with incomplete data were excluded from the statistical analysis.

For the statistical analysis the cohort was divided into statin users and statin non-users. The main outcomes to analyze were Disease Free Survival (DFS) and Overall Survival (OS) measured in months. Statistical analysis was performed using SPSS v20.0. ANOVA test was used for quantitative variables and X^2 test for qualitative variables. Kaplan-Meier curves were constructed for survival analysis. A p value < 0.05 was considered to be statistically significant.

The present study was approved by the Ethics Committee of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (REF. 146)

Results

One hundred and twenty-one (121) patients met the inclusion criteria. Mean age of the cohort was 53.7 (±12.04) years. The majority of patients were in stage III (55.4%), followed in frequency by stages I and IV (20.7% each) and finally stage II (2.5%). The most frequent histologic subtype was papillary serous, present in 70% of the cases. Optimal cytoreduction was obtained in 68% of patients.

Thirteen patients (10.7%) were receiving statins, including atorvastatin, pravastatin and rosuvastatin. There was no statistic difference among age (p=0.25), clinical stage (p=0.72), histologic subtype (p=0.12) or rate of optimal cytoreduction between statin users and non-users (69.2 vs 67.9%, p=0.59). Dyslipidemias could be associated with comorbidities that could affect survival; in this cohort only type 2 diabetes mellitus and malnutrition (defined as seric albumin < 3.5 g/dL) were documented, showing statistical difference only in the incidence of diabetes between groups (p=0.026) (Table 1).

The mean disease-free survival was 34.8 months for statin users and 25.1 months for non-users (p=0.47), while the mean overall survival was 55.7 months for statin users and 48.3 months for non-users (p=071). In the clinical stage subgroup analysis, it was noted that for patients with stage IIIC, the mean DFS was 40.6 months for statin users, with 11.49 months for non-users (p= 0.000), while the median OS was 81.2 months for statin users and 36.8 months for non-users (p=0.065) (Figures 1A and 1B).

Another factor significantly associated with worse DFS and OS within all statin users compared with no statin users was hypoalbuminemia (Figure 2A and 2B) with 19.09 months compared to 35.03 months in DFS (p= 0.000) and 43.13 months compared to 52.94 months in OS (p= 0.004).

Discussion

The objective of this article was to describe the association between statin use and survival of patients with diagnosis of EOC. To investigate it we performed a retrospective search of patient files with EOC diagnosis that underwent standard treatment (cytoreductive surgery plus chemotherapy) with concomitant statin consumption. Our most relevant findings where that, in stage IIIC patients, statin use was associated with a statistically significant longer DFS, as well as a tendency towards statistical significance for longer OS compared to non-users.

There have been several studies that highlight this association. It has been shown both *in vivo* and *in vitro* that statins inhibit tumor growth and promote apoptosis in a variety of cancers, including melanoma [8], glioma [9], neuroblastoma [10] and leukemia [11]. Table 2 pools the published articles that focus on the effect of statins in DFS and OS, specifically in ovarian cancer. It is important to note that some studies did not find a statistically significant difference between statin-users and non-users in patients with EOC [12-14]. Of the studies that found a statistically significant difference, only one is a prospective cohort [15], one is a case-control study [16]and three more are retrospective cohorts [17-19].

The heterogeneous results of these studies might be partly explained by the pharmacological differences among the

statins used, such as half-life and lipophilic structure, factors that have shown to impact apoptotic induction *in vivo* [20], as well as consumption time prior to oncological diagnosis and adherence to statin treatment afterwards.

Hypoalbuminaemia, as has been shown in previous systematic reviews and meta-analysis [21], was associated with a statistically significant lower DFS and OS. This association suggests that patients with hypoalbuminemia could benefit from a nutritional intervention prior and during oncologic treatment.

Conclusion

Our results show a positive association between statin use and longer DFS and OR in patients with CEO.

The present study is limited by its retrospective nature and small number of patients. There are other published studies with similar findings. The scarce side effects and wide availability are attractive factors to include this type of drugs as part of the adjuvant treatment for ovarian cancer patients. Other studies with higher statistical power, such as larger randomized controlled trials, are required to further study the effect of statins.

Figures

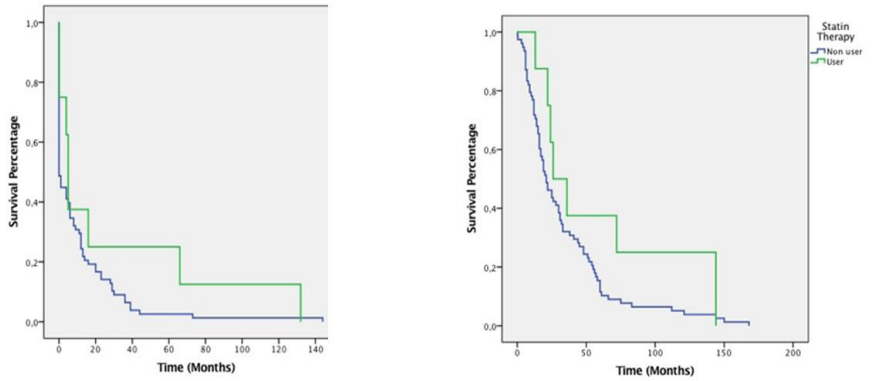

Figure 1: Kaplan-Meier curve for Stage III epithelial ovarian cancer patients.

Figure 1(A): Kaplan-Meier curve of Disease-Free Survival for Stage III epithelial ovarian cancer patients comparing statin (Green line) vs no statin users (Blue line).

Figure 1(B): Kaplan-Meier curve of Overall Survival for Stage III epithelial ovarian cancer patients comparing statin (Green line) vs no statin users (Blue line).

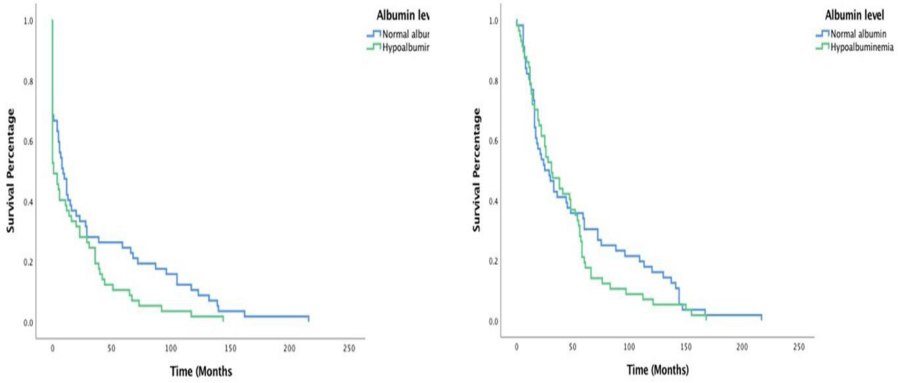

Figure 2(A): Kaplan-Meier curve of Disease-Free Survival for epithelial ovarian cancer patients comparing normal albumin levels (Blue line) vs hypoalbuminemia (Green line).

Figure 2(B): Kaplan-Meier curve of Overall Survival for epithelial ovarian cancer patients comparing normal albumin levels (Blue line) vs hypoalbuminemia (Green line).

Tables

Table 1: Patient characteristics: statin users versus non-users.

	Statinusers (n=13)	Non-users (n=108)	*p*
Mean age (years)	55.15(±10.1)	53.56 (±12.2)	0.25
Body Mass Index(kg/m2)	25.06(±3.7)	25.78(±4.8)	0.66
Comorbidities			
Diabetes mellitus	4 (30.7%)	8 (7.47%)	0.026
Hypoalbuminemia	6(46.1%)	51(47.2%)	0.5R
OB/GYN history			
Age at menarche (years)	13.2(±1.9)	12.9(±2)	0.52
Gravidity (n)	3(±2.2)	2.8(±2.8)	0.23
Oral contraceptives (%)	4(30.7%)	17(15.8%)	0.16
Postmenopause (%)	10(76.9%)	68(62.9%)	0.26
Clinical stage (%)			
I	4(30.7%)	21(19.62%)	0.72
II	0	3(2.8%)	
III	6(46.15%)	61(57%)	
IV	3(23.07%)	22(20.56%)	
Histologic subtype (%)			
Papillary serous	6(46.1%)	75(70%)	0.12
Mucinous	2(15.38%)	4(3.7%)	
Endometrioid	5(38.46%)	20(18.69%)	
Clear cells	0	1(0.93%)	
Other	0	7(6.54%)	
Cytoreduction (%)			
Optimal	9(69.2%)	72(67.9%)	0.59
Suboptimal	4(30.77%)	34(32%)	
Chemotherapy(%)			
Neoadjuvant	4(30.7%)	40(37%)	0.44
Adjuvant	8(61.5%)	69(63%)	0.51

Table 2: Studies that evaluate the effects of statins on survival in patients with ovarian cancer.

Authors	Country	Type of study	Cases	Statin users	Clinical stage	Histologic subtype	Treatment	Evaluated outcome	Conclusions
Chen HY et al (12)	China	Retrospective cohort	60	30 (50%)	III/IV	Epithelial/non-epithelial	CRS + adjuvant CHT	OS	No difference found
Bar et al (13)	Israel	Retrospective cohort	143	43 (30%)	I-IV	NS	CRS + neo/ adjuvant CHT	DFS OS	No difference found.
Verdoot et al (14)	Denmark	Retrospective cohort	4,419	476 (11%)	I-IV	Papillary serous, endometrioid, clear cells, mucinous	-	OS DSS	No difference found
Wang et al (15)	USA	Prospective cohort	230	47 (20%)	-	-	-	DSS	Improved survival in statin users
Lavie et al (16)	Israel	Case-control study	126 cases, 126 controls	38 (30.2%)	-	-	-	Ovarian cancer risk OS	Improved OS in statin users
Elmore RG et al (17)	USA	Retrospective cohort	126	17 (14%)	III/IV	OEC	CRS + adjuvant CHT	DFS OS	Improved survival in statin users
Vogel TJ et al (18)	USA	Retrospective cohort	1,431	609 (42%)	I-IV	NS	CRS + neo/ adjuvant CHT	OS DSS	Improved survival in statin users
Habis M et al (19)	USA	Retrospective cohort	442	68 (15%)	I-IV	Papillary serous, endometrioid, clear cells, mucinous	CRS + adjuvant CHT	DFS DSS	Improved survival in statin users with non-papillary serous EOC
Clemente-Gutiérrez et al	Mexico	Retrospective cohort	121	13	I-IV	EOC	CRS + neo/ adjuvant CHT	DFS OS	Improved survival in statin users

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