Original Article

Clinical Impact of Selective and Nonselective Beta-Blockers on Survival in Patients With Ovarian Cancer

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BACKGROUND: Preclinical evidence has suggested that sustained adrenergic activation can promote ovarian cancer growth and metastasis. The authors examined the impact of beta-adrenergic blockade on the clinical outcome of women with epithelial ovarian, primary peritoneal, or fallopian tube cancers (collectively, epithelial ovarian cancer [EOC]). **METHODS:** A multicenter review of 1425 women with histopathologically confirmed EOC was performed. Comparisons were made between patients with documented beta-blocker use during chemotherapy and those without beta-blocker use. **RESULTS:** The median age of patients in the current study was 63 years (range, 21-93 years). The sample included 269 patients who received beta-blockers. Of those, 193 (71.7%) were receiving beta-1–adrenergic receptor selective agents, and the remaining patients were receiving nonselective beta antagonists. The primary indication for beta-blocker use was hypertension but also included arrhythmia and postmyocardial infarction management. For patients receiving any beta-blocker, the median overall survival (OS) was 47.8 months versus 42 months for nonusers (P =.04). The median OS based on beta-blocker receptor selectivity was 94.9 months for those receiving nonselective beta-blockers versus 38 months for those receiving beta-1–adrenergic receptor selective agents (P<.001). Hypertension was associated with decreased OS compared with no hypertension across all groups. However, even among patients with hypertension, a longer median OS was observed among users of a nonselective beta-blocker compared with nonusers (38.2 months vs 90 months; P<.001). **CONCLUSIONS:** Use of nonselective beta-blockers in patients with EOC was associated with longer OS. These findings may have implications for new therapeutic approaches. ***Cancer*** **2015;000:000-000.** *© 2015 American Cancer Society.*

KEYWORDS: ovarian cancer, beta-blockers, survival, selective, nonselective.

INTRODUCTION

The role of the adrenergic system in epithelial ovarian cancer (EOC) carcinogenesis makes it an attractive target for the treatment of ovarian cancer. Reverse transcriptase-polymerase chain reaction studies have demonstrated constitutive expression of adrenergic receptors in the cell lines studied.[1] Extensive preclinical data have firmly established that the activation of the receptors results in the growth and progression of ovarian cancer.[1-4] In one study, norepinephrine and isoproterenol (an adrenergic agonist) significantly enhanced the production of vascular endothelial growth factor, which plays a crucial role in angiogenesis.[1] Propranolol, a nonselective beta blocker (NSBB), blocked the production of vascular endothelial growth factor.

In another in vitro study, norepinephrine and epinephrine (beta-adrenergic receptor agonists) were found to increase the invasive potential of ovarian cancer cells, but this effect was abrogated by propranolol. Norepinephrine also increased tumor cells' expression of matrix metalloproteinase (MMP)−2 and MMP-9, and pharmacological blockade of MMPs inhibited the effects of norepinephrine on the invasive potential of tumor cells.[2] In an orthotopic mouse model, daily restraint stress resulted in higher tissue catecholamine levels, greater tumor burden, and a more infiltrative

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TABLE 1. Demographic and Disease Characteristics[a]

Characteristic	Beta-Blocker Nonusers (N = 1156)	Beta-Blocker Users (N = 269)	*P*	Nonselective Beta-Blocker Users (N = 75)	*P*
Median age (range), y	61.6 (21.9-93.0)	68 (39-87.6)	<.001	65 (42-84)	<.001
Race					
White	583 (86.4%)	135 (89.4%)	.352	38 (86.4%)	.521
Nonwhite	92 (13.6%)	16 (10.6%)		6 (13.6)	
Unknown	481	118		31	
Stage of disease					
I/II	112 (9.7%)	28 (10.4%)	.733	9 (12%)	.755
III/IV	1044 (90.3%)	241 (89.6%)		66 (88%)	
Histology					
Serous	932 (80.6%)	223 (82.9%)	.437	63 (84%)	.723
Nonserous	224 (19.4%)	46 (17.1%)		12 (16%)	
BMI, kg/m^2					
Mean (SD)	27.8 (6.4)	29.7 (7.0)	<.001	29.4 (6.9)	<.001
Neoadjuvant therapy	96 (8.3%)	38 (14.1%)	.005	10 (13.3%)	.013
Cytoreduction					
Optimal (<1 cm)	789 (69.5)	181 (69.9%)	.940	59 (79.7%)	.100
Suboptimal	347 (30.5%)	78 (30.1%)		15 (20.3%)	
Missing data	20	10		1	
Comorbidities					
Hypertension	350 (30.3%)	250(92.9%)	<.001	68 (90.7%)	<.001
Diabetes	63 (5.4%)	22 (8.2%)	.114	8 (10.7%)	.118

Abbreviation: BMI, body mass index; SD, standard deviation.
[a] Data are shown as the number of patients (%) unless otherwise specified.

pattern of ovarian cancer. These effects were mediated primarily through adrenergic receptor-β_2 (ADRB2) activation of the protein kinase A signaling pathway. Tumors in these stressed animals demonstrated increased vascularization and enhanced expression of vascular endothelial growth factor, MMP-2, and MMP-9, effects that could be reversed by propranolol.[3]

This extensive preclinical evidence that adrenergic signaling promotes the growth of ovarian cancer, combined with similar clinical evidence for cancers in other organs such as the breast, pancreas, and colon, suggests that there could be clinical benefit in evaluating the use of beta-blockers on survival in patients with ovarian cancer.[4] There are several studies that have investigated the impact of beta-blocker use. These studies have had conflicting conclusions, which may be due, in part, to small patient numbers. The lack of attention to beta-blocker selectivity must also be considered as an explanation for the varying results.[5-7] At an in vitro level, the positive effects of beta blockade on ovarian cancer rely on ADRB2 inhibition. However, ADRB1-selective beta-blockers (SBBs) are more commonly prescribed than NSBBs, and populations with greater SBB use are unlikely to demonstrate a benefit from their beta-blocker use.[8] To examine the impact of selective versus nonselective ADRB blockade on patient survival, we conducted a multi-institutional retrospective cohort study of women with newly diagnosed epithelial ovarian, fallopian tube, or primary peritoneal cancer (collectively referred to as EOC).

MATERIALS AND METHODS

Study Design

A multi-institutional retrospective chart review was conducted on all patients with EOC who were diagnosed and treated with at least 1 cycle of platinum-based doublet chemotherapy from 2000 to 2010 at 4 institutions (The University of Texas MD Anderson Cancer Center [Houston, Tex], Washington University School of Medicine [St. Louis, Mo], Mayo Clinic [Rochester, Minn], and Mercy Medical Center [Baltimore, Md]). Institutional Review Board approval was obtained at all participating institutions. Patient charts, both electronic and paper, were reviewed for demographic information, the presence of hypertension or diabetes mellitus, tumor characteristics, cancer treatments, surgical outcome (optimal cytoreduction indicates <1 cm of residual disease), use of beta-blockers, and survival data. Use of beta-blockers was defined as any documentation of beta-blocker use in the medical record during neoadjuvant chemotherapy (NACT) or adjuvant chemotherapy (ACT). Overall survival (OS) was measured from the date of diagnosis to the date of death from any cause that was confirmed by patient chart or the Social Security Death Index. The OS of patients with different prognostic factors was determined in addition to the OS effect of beta-blocker use. Progression-free survival calculations were not conducted due to all institutions not reporting these data, but disease-specific survival modeling was performed.

TABLE 2. Proportional Hazards Models With Term for Any Beta-Blocker Use

	OS			Disease-Specific Survival		
	HR	P^a	95% CI	HR	P^a	95% CI
Beta-blockers (reference: no beta-blockers)	0.26	**<.0001**	0.19-0.37	0.24	**<.0001**	0.17-0.34
Beta-blocker ×ln(time)	1.70	**<.0001**	1.31-2.19	1.82	**<.0001**	1.39-2.38
Age	1.02	**<.0001**	1.01-1.02	1.02	**<.0001**	1.01-1.02
Race: nonwhite (reference: white)	1.00	.979	0.75-1.32	0.98	.899	0.74-1.30
Race: unknown (reference: white)	1.04	.829	0.74-1.47	1.02	.895	0.72-1.45
Stage III/IV	3.26	<.0001	2.19-4.84	3.23	<.0001	2.17-4.80
Serous histology	0.89	.221	0.73-1.07	0.89	.233	0.74-1.08
BMI: 25-29.9 (reference: BMI <25)	0.95	.588	0.78-1.15	0.95	.605	0.79-1.15
BMI: ≥30 (reference: BMI <25)	1.16	.135	0.96-1.40	1.15	.158	0.95-1.39
BMI: unknown (reference: BMI <25)	1.27	.023	1.03-1.57	1.27	.025	1.03-1.56
Neoadjuvant therapy	1.92	<.0001	1.42-2.60	1.94	<.0001	1.43-2.62
Diabetes	0.96	.773	0.72-1.27	0.98	.869	0.74-1.29
Hypertension	1.79	<.0001	1.50-2.13	1.79	<.0001	1.50-2.13
Y 1						
Beta-blockers and hypertension	0.47	**<.0001**	0.34-0.65	0.43	**<.0001**	0.31-0.61
Beta-blockers and no hypertension	0.26	**<.0001**	0.19-0.37	0.24	**<.0001**	0.17-0.34
No beta-blockers and hypertension	**1.79**	**<.0001**	1.5-2.13	**1.79**	**<.0001**	1.50-2.13
Y 5						
Beta-blockers and hypertension	1.10	.431	0.86-1.41	**1.13**	.318	0.89-1.45
Beta-blockers and no hypertension	0.62	**.0005**	0.47-0.81	0.63	**.0010**	0.48-0.83
No beta-blockers and hypertension	**4.19**	**<.0001**	2.71-6.49	**4.70**	**<.0001**	2.98-7.40

Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; HR, hazards ratio; OS, overall survival.
[a] Bold type indicates statistical significance.

Statistical Analysis

Patients were first evaluated using descriptive statistics to summarize the demographic and clinical characteristics of the 2 groups: those who used beta-blockers and those who did not. Fisher exact tests were used to compare groups with respect to distribution of categorical data, and a 2-sample Student *t* test was used to compare groups with respect to the means for continuous data. If normality assumptions for the Student *t* test were not met, the nonparametric Mann-Whitney *U* test was used to compare groups. Using the Kaplan-Meier method, OS was estimated for groups by beta-blocker use and type of beta-blocker used (SBB vs NSBB).[9] Log-rank tests were conducted to examine differences by beta-blocker use and type.[10] Proportional hazards models were created using the covariates listed in Tables 1 to 5 and 95% confidence intervals (95% CIs) as well as *P* values were calculated.[11] *P* values <.05 were considered to be statistically significant; *P* values were not adjusted for multiple comparisons.

RESULTS

Demographic and Disease Characteristics

From the 4 participating institutions, 1425 patients with EOC were identified as being eligible for inclusion in the current study. Demographic, disease, and treatment characteristics are shown in Table 1. Beta-blocker users were older, had higher body mass indices (BMIs), and were more likely to have hypertension compared with nonusers. Greater than 90% of patients received upfront surgery followed by ACT. Patients receiving NACT were more likely to be receiving beta-blockers ($P = .005$).

Prognostic Factors

Age, FIGO stage of disease, sequence of therapy, surgical outcome, histology, BMI, tumor grade, and race were evaluated for effect on OS for all patients. Older patients (those aged >65 years) had a decreased OS rate ($P < .001$). Patients with stage III or IV disease at the time of presentation were found to have a shorter median OS compared with those presenting with stage I or II disease ($P < .001$). Patients receiving NACT had decreased survival when compared with those who underwent upfront surgery followed by chemotherapy (28.7 months vs 45.6 months; $P < .001$). Optimal interval cytoreduction (<1 cm of residual disease) was associated with an increased median OS for patients treated with NACT compared with patients treated with NACT who had a suboptimal surgery (37.4 months vs 22.6 months; $P = 0.002$). Patients with serous histology who received ACT had a shorter median OS compared with those with nonserous histology who received ACT (44.5 months vs 55.9 months; $P = .035$). However, histology made no difference in OS for those who received NACT (30.5 months vs 28.4 months; $P = .51$). BMI also was found to have no effect on OS

TABLE 3. Proportional Hazards Model With Terms for Specific Beta-Blocker Type

	OS			Disease-Specific Survival		
	HR	P[a]	95% CI	HR	P[a]	95% CI
Selective beta-blockers (reference: no beta-blockers)	0.32	**<.0001**	0.22-0.45	0.29	**<.0001**	0.20-0.42
Selective beta-blocker ×ln(time)	1.87	**<.0001**	1.40-2.50	2.05	**<.0001**	1.51-2.79
Nonselective or combination (reference: no beta-blockers)	0.08	**<.0001**	0.03-0.22	0.08	**<.0001**	0.03-0.22
Nonselective or combination ×ln(time)	2.47	**.010**	1.25-4.91	2.48	**.010**	1.25-4.93
Age	1.02	<.0001	1.01-1.02	1.02	<.0001	1.01-1.02
Race: nonwhite (reference: white)	0.96	.798	0.73-1.28	0.95	.731	0.72-1.26
Race: unknown (reference: white)	1.01	.937	0.72-1.43	1.00	.990	0.71-1.42
Stage III/IV	3.29	<.0001	2.21-4.91	3.27	<.0001	2.19-4.87
Serous histology	0.87	.151	0.72-1.05	0.87	.156	0.72-1.05
BMI: 25-29.9 (reference: BMI <25)	0.97	.782	0.80-1.18	0.97	.795	0.80-1.18
BMI: ≥30 (reference: BMI <25)	1.14	.179	0.94-1.38	1.13	.211	0.93-1.37
BMI: unknown (reference: BMI <25)	1.28	**.020**	1.04-1.58	1.28	.023	1.03-1.57
Neoadjuvant therapy	1.96	<.0001	1.45-2.65	1.98	<.0001	1.46-2.68
Diabetes	0.99	.958	0.75-1.31	1.01	.945	0.76-1.34
Hypertension	1.79	<.0001	1.50-2.13	1.79	<.0001	1.50-2.14
Y 1						
Selective beta-blockers and hypertension	0.57	**.002**	0.40-0.81	0.51	**.0004**	0.36-0.74
Selective beta-blockers and no hypertension	0.32	**<.0001**	0.22-0.45	0.29	**<.0001**	0.2-0.42
Nonselective/combination beta-blockers and hypertension	0.14	<.0001	0.05-0.39	0.14	**.0001**	0.05-0.39
Nonselective/combination beta-blockers and no hypertension	0.08	**<.0001**	0.03-0.22	0.08	**<.0001**	0.03-0.22
Y 5						
Selective beta-blockers and hypertension	**1.57**	**.002**	1.18-2.09	**1.64**	**.0007**	1.23-2.18
Selective beta-blockers and no hypertension	0.88	.408	0.64-1.20	0.91	.578	0.67-1.25
Nonselective/combination beta-blockers and hypertension	0.60	**.018**	0.40-0.92	0.61	**.020**	0.4-0.92
Nonselective/combination beta-blockers and no hypertension	0.34	**<.0001**	0.22-0.52	0.34	**<.0001**	0.22-0.53

Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; HR, hazards ratio; OS, overall survival.
[a] Bold type indicates statistical significance.

except among patients treated with NACT (P =.024). Race and tumor grade had no effect on OS.

The presence of comorbidities was also evaluated for its effect on survival in the overall group. Hypertension was associated with decreased survival compared with normal blood pressure (40.1 months vs 47.4 months; P<.001). Diabetes mellitus appeared to have no significant effect on OS (39.8 months vs 43.4 months; P =.503).

Disease-Specific Survival by Beta-Blocker Use

Because progression-free survival data were not available from all sites, models were created to examine disease-specific survival (DSS) based on any use of beta-blockers (Table 2) and specific types of beta-blockers (Table 3). During the first year, patients who used any type of beta-blocker had improved DSS regardless of whether they had hypertension compared with nonusers (P<.0001). By the fifth year, patients who received SBB and had hypertension had a statistically significant increase in disease-specific mortality (hazard ratio [HR], 1.64; 95% CI, 1.23-2.18 [P =.0007]). Patients who took SBBs and did not have hypertension had no difference in disease-specific mortality. Patients treated with NSBB continued to have improved DSS regardless of whether they had hypertension, but they fared especially well if they had no hypertension (HR, 0.34; 95% CI, 0.22-0.53 [P<.0001]).

OS by Beta-Blocker Use

The influence of beta-blocker use on OS in all patients was examined alone and in relation to the presence of comorbidities, and the results are outlined in Table 4. Proportional hazards models stratified by institution were created using the covariates shown in Table 1. A test of the proportional hazards assumption indicated that this was violated for beta-blocker use and optimal cytoreduction. Therefore, cytoreduction was included in the model as a stratification factor and an interaction term for beta-blocker use by the natural log of time was included in the model to adjust for these violations. Beta-blocker use of any kind was associated with a longer median OS than nonuse (47.8 months vs 42 months; P =.036). When further classifying patients based on beta-blocker selectivity (SBB vs NSBB), no difference in the median OS was observed between SBB users and nonusers (38 months vs 42 months; P =.196). However, patients receiving NSBB had a longer median OS than nonusers (94.9 months vs 42 months; P<.001). Because optimal cytoreduction is a known prognostic factor for survival and differed between the patients treated with SBBs (69.9%) and those treated

TABLE 4. Analyses of Beta-Blocker Use and Comorbidities for OS in Patients With EOC[a]

Patient Population	Beta-Blocker Use	Median Time to Event, Months	Log-Rank *P*				
			No Beta-Blocker Versus Beta-Blockers	No Beta-Blockers, SBB, NSBB	No Beta-Blockers Versus SBB	No Beta-Blockers Versus NSBB	SBB Versus NSBB
All patients	No beta-blockers (n = 1156)	42	.036	<.001	.196	<.001	<.001
	Any beta-blocker (n = 268)	47.8					
	SBBs (n = 193)	38.0					
	NSBBs (n = 75)	94.9					
No diabetes	No beta-blockers (n = 1093)	42.4	.029	<.001	.328	<.001	<.001
	Any beta-blockers (n = 246)	48.5					
	SBBs (n = 179)	38.2					
	NSBBs (n=67)	94.9					
Diabetes	No beta-blockers (n = 63)	38.4	.987	.079	.183	.183	.001
	Any beta-blockers (n = 22)	47.4					
	SBBs (n = 14)	31.2					
	NSBBs (n = 8)	67.7					
No hypertension	No beta-blockers (n = 806)	47.9	.715	.002	.003	.057	.001
	Any beta-blockers (n = 18)	42.8					
	SBBs (n = 11)	33.4					
	NSBBs (n = 7)	112					
Hypertension	No beta-blockers (n = 350)	34.2	<.001	<.001	.007	<.001	<.001
	Any beta-blockers (n = 250)	49.0					
	SBBs (n = 182)	38.2					
	NSBBs (n = 68)	90.0					

Abbreviations: EOC, epithelial ovarian cancer; NSBB, nonselective beta-blockers; OS, overall survival; SBB, selective beta-blockers.
[a] One beta-blocker user was excluded from OS analysis because of missing information.

with NSBBs (79.7%), this finding was analyzed and the importance of taking any type of beta-blocker with the use of optimal or suboptimal cytoreduction remained in the first year except for patients with SBB and hypertension, as shown in Table 5. By year 5, only NSBB conferred a benefit to women without hypertension who underwent optimal cytoreduction (HR, 0.31; 95% CI, 0.10-0.98 [$P = .046$]) and those who underwent suboptimal cytoreduction (HR, 0.28; 95% CI, 0.17-0.45 [$P<.0001$]). Additional comparisons were made based on beta-blocker use and sequence of chemotherapy (NACT vs ACT). Beta-blockers users had an OS benefit compared with nonusers, regardless of whether they underwent upfront cytoreductive surgery followed by ACT (49.9 months vs 44.5 months; $P = .042$) or they received NACT (37.9 months vs 26.3 months; $P = .048$).

OS by Beta-Blocker Use and Comorbidities

Patients without diabetes had a significantly longer median OS if they received an NSBB compared with nonusers of beta-blockers (94.9 months vs 42.4 months; $P<.001$) and a nonsignificant decrease in median OS if an SBB was used (38.2 months) (Table 4). Among patients with diabetes, NSBB users had a significant increase in their median OS compared with SBB users (Table 4).

Among beta-blocker users, the presence of hypertension had no significant effect on the median OS compared with patients with normal blood pressure (49 months vs 42.8 months; $P = .54$). Among patients without hypertension, those who received an SBB had a shorter median OS compared with those who did not use beta-blockers (33.4 months vs 47.9 months; $P = .003$). The median OS of normotensive NSBB users (112 months; $P = .057$) was not statistically significant compared with that of nonusers (Table 4), but when compared with SBB users with normal blood pressure a significant improvement was observed (33.4 months vs 112 months; $P = .001$). The OS improvement for normotensive NSBB users compared with nonusers represented the largest numerical difference in median OS (64.1 months).

For hypertensive patients, any beta-blocker use was associated with a longer median OS compared with nonusers (49 months vs 34.2 months; $P<.001$). Hypertensive patients receiving SBBs had a longer OS than nonusers (38.2 months vs 34.2 months; $P = .007$). However, NSBB users were observed to have a longer median OS (90 months; $P<.001$) than either users of SBBs or nonusers with elevated blood pressure (Fig. 1). Hypertension appeared to have no statistically significant effect on OS in patients treated with ACT using beta-blockers (39.6 months vs 50.4 months; $P = .517$). Among patients

TABLE 5. Proportional Hazards Model by Optimal Cytoreduction for OS With Terms for Specific Beta-Blocker Type

	Optimal Cytoreduction			Suboptimal Cytoreduction		
	HR	P^a	95% CI	HR	P^a	95% CI
Selective beta-blockers (reference: no beta-blockers)	**0.26**	**<.0001**	0.14-0.50	0.36	**<.0001**	0.23-0.55
Selective beta-blocker ×ln(time)	**3.14**	**.0001**	1.75-5.66	1.45	**.032**	1.03-2.03
Nonselective or combination (reference: no beta-blockers)	**0.09**	**.025**	0.01-0.74	0.07	**<.0001**	0.02-0.21
Nonselective or combination ×ln(time)	2.14	.345	0.44-10.43	2.42	**.024**	1.13-5.22
Age	1.01	.063	1.00-1.02	1.02	<.0001	1.01-1.03
Race: nonwhite (reference: white)	1.11	.610	0.74-1.68	0.91	.654	0.62-1.35
Race: unknown (reference: white)	1.00	.987	0.57-1.76	1.02	.945	0.64-1.60
Stage III/IV	1.72	.230	0.71-4.19	3.68	<.0001	2.35-5.78
Serous histology	0.75	.121	0.52-1.08	0.91	.393	0.72-1.14
BMI: 25-29.9 (reference: BMI <25)	1.03	.872	0.74-1.43	0.94	.618	0.74-1.19
BMI: ≥30 (reference: BMI <25)	1.41	.035	1.02-1.93	1.03	.826	0.81-1.31
BMI: unknown (reference: BMI <25)	1.35	.083	0.96-1.91	1.25	.109	0.95-1.63
Neoadjuvant therapy	1.34	.442	0.63-2.86	2.16	<.0001	1.54-3.02
Diabetes	0.71	.174	0.44-1.16	1.19	.332	0.84-1.69
Hypertension	1.30	.063	0.99-1.72	2.23	<.0001	1.78-2.80
Y 1						
Selective beta-blockers and hypertension	0.34	**.0008**	0.18-0.64	0.80	.291	0.52-1.22
Selective beta-blockers and no hypertension	0.26	**<.0001**	0.14-0.50	0.36	**<.0001**	0.23-0.55
Nonselective/combination beta-blockers and hypertension	0.12	**.046**	0.01-0.96	0.15	**.001**	0.05-0.47
Nonselective/combination beta-blockers and no hypertension	0.09	**.025**	0.01-0.74	0.07	**<.0001**	0.02-0.21
Y 5						
Selective beta-blockers and hypertension	**2.16**	**.007**	1.24-3.79	**1.45**	**.033**	1.03-2.03
Selective beta-blockers and no hypertension	1.66	.084	0.93-2.96	0.65	**.026**	0.44-0.95
Nonselective/combination beta-blockers and hypertension	0.40	.124	0.13-1.28	0.62	**.039**	0.4-0.98
Nonselective/combination beta-blockers and no hypertension	0.31	**.046**	0.10-0.98	0.28	**<.0001**	0.17- 0.45

Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; HR, hazards ratio; OS, overall survival.
[a] Bold type indicates statistical significance.

treated with NACT who did not receive beta-blockers, those with hypertension had a shorter median OS compared with normotensive patients (19.7 months vs 30.5 months; $P<.001$). This negative effect of hypertension on OS was not observed in the patients treated with NACT who were being treated with beta-blockers (37.9 months vs 42.8 months; $P=.80$).

DISCUSSION

The prolonged OS of patients with EOC who are receiving beta-blockers, especially NSBB, is an important finding, and to our knowledge the current study is the first to demonstrate an OS benefit in relation to beta-blocker selectivity in these patients. The ability to improve the survival of patients with EOC via ADRB2 blockade using beta-blockers would be the culmination of years of research into the biology and pathogenesis of EOC. Particularly interesting is the finding that beta-blocker users in the current study presented at a higher stage of disease, had an increased average BMI, and were more likely to be hypertensive. All these factors were associated with decreased survival, yet those who received beta-blockers had either equivalent or improved OS. Further examination revealed that NSBB users had improved OS regardless of the presence of prognostic factors or comorbidities shown to decrease OS. This was not true for patients who took SBBs; in some cases, a decreased OS was observed. Although further study is needed, these results highlight the importance of ADRB2 in ovarian carcinogenesis and the usefulness of NSBB.

The current study is limited by its retrospective design and the resulting inability to document the duration of beta-blocker use and dosages used by patients with EOC. Although it would be ideal to have better documentation of beta-blocker use in the current study population, the finding that improvement was noted in patients who used beta-blockers for any duration at any dose during their chemotherapy is promising. The validity of the current study findings is improved due to the study being multi-institutional with a large cohort of patients with EOC. Most importantly, the stratification of patients by beta-blocker use and selectivity makes it unique among all other studies examining the impact of the use of beta-blockers among patients with ovarian cancer.[5-7,12]

In contrast to the findings of the current study, Eskander et al found no difference in progression-free

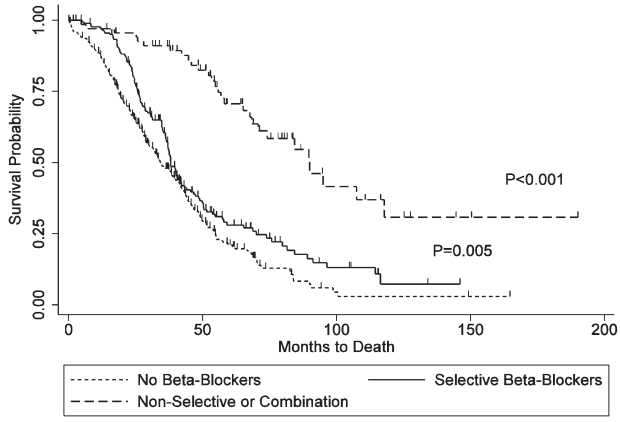

Figure 1. Kaplan-Meier overall survival curves of patients with hypertension based on beta-blocker use (nonusers, users of selective beta-blockers, and users of nonselective beta-blockers). The median overall survival was 34.2 months for nonusers, 38.2 months (P =.005) for users of selective beta-blockers, and 90 months (P<.001) for users of nonselective beta-blockers.

survival or OS between patients with EOC who did or did not use beta-blockers.[6] Similarly, when Johannesdottir et al stratified the Danish Cancer Registry of >6000 patients with ovarian cancer by current (≤90 days), past (>90 days), and never-use of beta-blockers, the authors found no difference in all-cause mortality.[7] To the best of our knowledge, none of these studies reported on the selectivity of the beta-blockers used. A multi-institutional European study that evaluated the impact of beta-blocker use in patients with platinum-sensitive, recurrent EOC did report the selectivity of beta-blockers used (approximately 10% of their population were receiving beta-blockers and of those, only 1.5% were receiving an NSBB), but did not stratify survival outcomes by beta-blocker selectivity.[12] Without stratification for beta-blocker selectivity, direct comparison of these conflicting results is difficult. In vitro studies have shown that it is specifically ADRB2 stimulation that contributes to ovarian cancer development and metastasis.[2-4,13] This is supported by the improvements in OS noted among patients receiving NSBB compared with those taking any beta-blocker. More telling is the finding that in some cases, patients taking an SBB had worsened survival. It is unclear why those taking SBB fared worse than those not taking beta-blockers, but it could be related to the increased age, higher median BMI, and presence of comorbidities in that group. Whether SBBs independently result in decreased OS will require further investigation. These results showcase the importance of ADRβ_2 in EOC pathogenesis and the potential for NSBBs to improve outcomes in all patients with EOC. Thus, it is necessary to stratify patients based on beta-blocker selectivity in future studies so that we may best understand how to incorporate NSBB into treatment to improve the outcomes of individual patients.

In studies examining the effects of beta-blockers on survival in patients with breast, lung, or ovarian cancer or melanoma, patients were taking beta-blockers for cardiac or other clinical indications and not for cancer therapy.[5-7,12,14,15] However, with mounting evidence of the potential impact of beta-blockers on the outcomes of patients with cancer, a prospective clinical trial is warranted to identify those patients who would benefit most from beta-blocker use and to identify the best beta-blocker for a specific tumor type based on adrenergic receptor expression. Tumor cell expression of ADRB could be used as a biomarker for selecting those patients who would benefit from a specific beta-blocker. Beta-blockers could then be used as an adjuvant therapy during surgical recovery and chemotherapy to decrease tumor angiogenesis, tumor growth, delays in wound healing, and metastasis.[15,16] Beta-blockers also may reduce cancer-related psychological distress in patients newly diagnosed with cancer.[15] Therefore, beta-blockers have the potential to impact not only cancer biology and immunology but also the psychological well-being of patients with cancer.

Because the biological effects and recommended dosing schedules of beta-blockers for hypertension are well known, adding these drugs to ACT should be relatively easy. However, beta-blockers are degraded by the enzyme cytochrome P450 2D6, and understanding of the activity of this enzyme may play a key role in identifying doses that are likely to have maximal clinical benefit. Several genetic polymorphisms in this gene exist, and variations in drug sensitivity that result from these polymorphisms may determine the individual pharmacokinetics for each patient to allow for dose optimization.[15]

There are currently 2 clinical trials that are evaluating the combination of chemotherapy and variable doses of propranolol on cancer biology as well as the effect of NSBBs on stress modulators in patients newly diagnosed with EOC.[18,19] The preliminary data from these feasibility trials will help us to design adequately powered, prospective, randomized clinical trials to determine whether NSBBs can improve outcomes for patients with EOC.

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CONFLICT OF INTEREST DISCLOSURES

Dr. Thaker has acted as a paid consultant for Incyte Pharmaceuticals and received research funding from Egen Pharmaceuticals.

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