

RESEARCH ARTICLE

Does Beta-blocker Therapy Improve the Survival of Patients with Metastatic Non-small Cell Lung Cancer?

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Abstract

Aim: To determine whether beta-blockers (BBs) improve the overall survival (OS) of patients with metastatic non-small cell lung cancer (NSCLC). **Materials and Methods:** The medical charts of 107 patients with metastatic NSCLC were retrospectively assessed. Thirty-five patients (BB group) using BBs during chemotherapy (CT) were compared with 72 controls [control=(C) group] who did not use BBs following the diagnosis of NSCLC. The histological tumor subtype, performance status (ECOG), age, gender, smoking status, comorbidities, other medications and chemotherapeutics that were received in any line of treatment were recorded. We compared the overall survival (OS) of the patients in the BB and C groups. **Results:** The mean age of the patients was 61 years (range 42-81 years) and all patients were administered CT. The BB group was more likely to have HT and IHD and was more likely to use RAS blockers ($p < 0.01$ for all) compared with the C group, as expected. The mean follow-up time was 17.8 months (range 1-102 months) for the entire group. The most commonly prescribed BB agent was metoprolol (80% of cases). At the time of the analysis, 74 (69%) of all patients had died. In the univariate analysis the median overall survival (OS) was 19.25 (± 2.87) months (95% CI: 13.62-24.88) in the BB group and 13.20 (± 2.37) months (95% CI: 8.55-17.85) in the C group ($p = 0.017$). However, the benefit of BBs on survival disappeared in the multivariate analysis. **Conclusions:** The use of BBs during CT may be associated with an improved OS for patients with metastatic NSCLC.

Keywords: Beta-blockers - non-small cell lung cancer - survival

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Introduction

Non-small cell lung cancer (NSCLC) is a common cause of cancer death worldwide, despite all of the current cancer therapeutics (Jemal et al., 2007). According to recent studies, beta-adrenergic signaling stimulates cancer growth (Al-Wadei et al., 2012; Cole and Sood, 2012). Preclinical studies have demonstrated that beta-adrenergic receptor (AR) signaling has strong stimulating effects in cancers of the colon (Masur et al., 2001; Wong et al., 2007), prostate (Palm et al., 2006), ovary (Sood et al., 2006; Thaker et al., 2006), breast (Drell et al., 2003) and pancreas (Al-Wadei et al., 2009). Regarding the impact of beta-blockers (BBs) on cancer survival, a recent study showed that BBs reduce the development of metastasis and recurrence in non-metastatic breast cancer and improve cancer-specific survival (Powe et al., 2010).

Nicotine, a major component of tobacco, activates an autocrine noradrenaline-initiated signaling cascade and may facilitate the growth and progression of NSCLC among smokers (Al-Wadei et al., 2012). Preclinical studies have shown that beta-adrenergic signaling could stimulate NSCLC growth (Schuller et al., 1999; Laag et al., 2006)

and that this effect could be reversed by BBs (both atenolol (Schuller and Cekanova, 2005; Laag et al., 2006) and propranolol (Al-Wadei et al., 2012), suggesting that agents interfering with the beta-adrenergic signaling cascade may be promising for the treatment of NSCLCs. Conversely, in a large retrospective study including patients with a variety of solid tumours (including NSCLC) showed that BBs do not improve 1-year survival compared with other anti-hypertensive drugs (Shah et al., 2011).

Most of the preclinical studies on the role of nicotine/beta adrenergic signaling in NSCLC are experimental (Schuller et al., 1999; Schuller and Cekanova, 2005; Laag et al., 2006; Al-Wadei et al., 2012). Although some data (Schuller and Cekanova, 2005; Laag et al., 2006; Al-Wadei et al., 2012) suggest the benefit of BBs in NSCLC, those studies usually focused on preventing metastasis rather than the survival effect after metastasis and are thus inadequate for use in clinical practice. No clinical data are available that show whether BBs have an impact on the survival of patients with metastatic NSCLC. The present study ($n = 107$) retrospectively compared the overall survival of patients with metastatic NSCLC according to the use of BBs during cancer therapy.

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Materials and Methods

Patients

This case-control study was performed by retrospectively screening 850 NSCLC patients diagnosed between 2003 and 2011. We identified 35 patients with metastatic NSCLC receiving a BB agent during chemotherapy (CT) at any time after the diagnosis of the malignancy. We evaluated whether the use of BBs (as clinically indicated) had an effect on survival by comparing these 35 patients with 72 age-, sex- and histological subtype-matched counterparts who did not use BBs at any time after the diagnosis of NSCLC [control (C) group]. While selecting appropriate controls, we planned to match the BB and C groups at a 1:2 ratio based on age, gender, ECOG performance status, stage and histological subtype. The most appropriate matching C group included two more patients than the preplanned number. Additionally, the C group comprised three more patients with an ECOG performance status of 2-3, two more patients older than 60 years, two adscititious males, one more squamous cell NSCLC patient and one more non-squamous cell NSCLC patients than initially planned. However, all of the clinicopathologic and demographic features of the C and BB groups were similar (Table 1). This study is a retrospective review of 107 patients with metastatic NSCLC who were diagnosed between 2003 and 2011. All of the patients enrolled in the study had pathologically confirmed NSCLC, distant metastasis and an ECOG performance status of 0-3 and received CT.

Table 1. Patient Characteristics and Comparison of the Beta-blocker (BB) and Control (C) Groups

	Control (%)	Beta-blocker (%)	p*
Number of patients	72 (67.3)	35 (32.5)	
Age (mean)	61	61	
Age:			0.89
≤60	36 (50)	18 (51.4)	
>60	36 (50)	17 (48.6)	
Gender:			0.97
Male	68 (94.4)	33 (94.3)	
Female	4 (5.6)	2 (5.7)	
ECOG:			0.63
0-1	64 (88.9)	30 (85.7)	
2-3	8 (11.1)	5 (14.3)	
Smoking:			0.96
Yes	66 (91.7)	32 (91.4)	
No	6 (8.3)	3 (8.6)	
Subtype:			0.96
Nonsquamous	47 (65.3)	23 (65.7)	
Squamous	25 (34.7)	12 (34.3)	
Comorbidity: (+) vs. (-)	35 (48.6)	29 (82.9)	0.001
Hypertension: (+) vs. (-)	15 (20.8)	20 (57.1)	<0.001
IHD: (+) vs. (-)	7 (9.7)	17 (48.6)	<0.001
Chronic heart failure: (+) vs. (-)	2 (2.8)	2 (5.7)	0.45
Arrhythmia: (+) vs. (-)	4 (5.6)	1 (2.9)	0.53
Diabetes mellitus: (+) vs. (-)	8 (11.1)	7 (20)	0.21
Chronic renal failure: (+) vs. (-)	1 (1.4)	2 (5.7)	0.2
COPD: (+) vs. (-)	6 (8.3)	2 (5.7)	0.62
RAS blocker: (+) vs. (-)	6 (8.3)	12 (34.3)	0.001
Ca blocker: (+) vs. (-)	5 (6.9)	2 (5.7)	0.89
Gemcitabine: (+) vs. (-)	46 (63.9)	28 (80)	0.09
Pemetrexed: (+) vs. (-)	14 (19.4)	9 (25.7)	0.45
Taxane: (+) vs. (-)	49 (68.1)	26 (74.3)	0.5
Etoposide: (+) vs. (-)	4 (5.6)	5 (14.3)	0.12
Erlotinib: (+) vs. (-)	12 (16.7)	6 (17.1)	0.95
Platinum: (+) vs. (-)	70 (97.2)	31 (88.6)	0.068
Vinorelbine: (+) vs. (-)	14 (19.4)	6 (17.1)	0.77
Last status:			0.42
Ex	48 (66.7)	26 (74.3)	
Alive	24 (33.3)	9 (25.7)	

*p=control vs betablocker

Patients with a history of another malignancy, who could not receive CT or with an ECOG performance status of 4 were excluded. The patient characteristics are summarized in Table 1.

Study covariates and outcomes

Data about the medications of the patients were recorded from their medical charts. Patients were included in the BB group if they used a BB agent during CT at any time after the diagnosis of NSCLC, and patients who did not receive a BB agent at any time after their cancer diagnosis were included in the C group. The histological tumor subtype, performance status (ECOG), age, gender, smoking status, comorbidities (hypertension (HT), ischemic heart disease (IHD), chronic obstructive pulmonary disease (COPD), and diabetes mellitus (DM)) and other medications, including renin-angiotensin system (RAS) blockers, calcium channel blockers (CCBs) and chemotherapeutics, that were received in any line of treatment, all of which may affect the outcome of lung cancer and thus confound the BB analysis, were recorded (Table 1). We analyzed the overall survival (OS), which was defined as the time elapsed from the date of diagnosis to the date of death. For OS, death was an event time. The follow-up time was defined as the time from the date of diagnosis to the date of death or last follow-up.

Statistical methods

The BB and C groups were compared using Pearson's chi-square or Fisher's exact tests (Table 1). The Kaplan-Meier method was used to estimate the survival outcomes of the two groups, and the groups were compared with the log-rank statistic. In addition, univariate analyses (UVA) including other parameters that may have impacted survival were assessed with the Kaplan-Meier method, and the groups were compared with the log-rank statistic (Table 2). Cox regression analysis were used to determine the association of BB intake with the survival outcomes in the multivariate analysis (MVA). In the MVA, confounders were included if they were significant at a 0.05 level in the UVA or thought to be important for survival or the BB effect. The results were expressed as the median OS±SE (standard error) and hazard ratios (HRs) with 95% confidence intervals (CIs). A p value of <0.05 was considered statistically significant; all tests were two-sided. All patients were included in the UVAs and MVA. The statistical analyses were conducted using SPSS version 16.

Results

The current study included 107 patients with metastatic NSCLC. Thirty-five patients (32.7%) received BBs during CT, and 72 controls (67.3%) did not receive BBs. The patient characteristics are listed in Table 1. The mean age of the patients was 61 years (range 42-81 years) in both the BB and C groups, and all patients were treated with CT. Most of the patients were male (94%) and smokers (91%) and had a non-squamous histology (65%) and good performance status (ECOG 1-2: 87%). Patients in the BB group were more likely to have HT (57.1 vs 20.8 %) and

Table 2. Univariate Analysis of Overall Survival (OS) for the Included Parameters

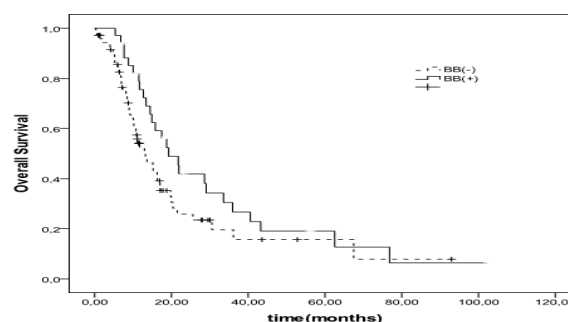
Variables	n events/ n total	Median OS (±SE)	p
Beta-blocker (+)	26/35	19.25 (2.87)	0.017
Beta-blocker (-)	48/72	13.2 (2.37)	
Gender Male	70/101	15.1 (1.55)	0.54
Gender Female	4/6	12.4 (3.2)	
Comorbidity (+)	44/64	15.21 (2)	0.72
Comorbidity (-)	30/43	16.26 (3.16)	
Hypertension (+)	27/35	15.21 (2.84)	0.75
Hypertension (-)	47/72	15.11 (1.76)	
IHD (+)	17/24	14.42 (2.23)	0.51
IHD (-)	57/83	15.21 (2)	
Chronic heart failure (+)	3/4	10.00 (1.59)	0.68
Chronic heart failure (-)	71/103	15.77 (1.66)	
Arrhythmia (+)	3/5	11.66 (2.43)	0.34
Arrhythmia (-)	71/102	15.77 (1.68)	
Diabetes (+)	11/15	11.00 (2)	0.21
Diabetes (-)	63/92	15.77 (1.37)	
Cerebrovascular event (+)	2/2	11.66	0.46
Cerebrovascular event (-)	72/105	15.21 (1.78)	
Chronic renal failure (+)	3/3	11.66 (0.34)	0.28
Chronic renal failure (-)	71/104	16.26 (1.84)	
COPD (+)	5/8	14.88 (5.98)	0.09
COPD (-)	69/99	15.77 (1.96)	
RAS blocker (+)	14/18	14.42 (2.89)	0.82
RAS blocker (-)	60/89	16.26 (1.89)	
CCBs (+)	6/7	10.18 (0.21)	0.24
CCBs (-)	68/100	16.26 (1.36)	
ECOG 0-1	66/94	15.11 (1.79)	0.85
ECOG 2-3	8/13	21.52 (6.38)	
Age ≤60	37/54	16.26 (1.9)	0.24
Age >60	37/53	14.42 (3.1)	
Subtype Nonsquamous	49/70	16.26 (1.56)	0.42
Subtype Squamous	25/37	11.49 (3.22)	
Smoking (+)	67/98	15.11 (1.53)	0.50
Smoking (-)	7/9	25.56 (1.18)	
Gemcitabine (+)	54/74	16.26 (2.2)	0.48
Gemcitabine (-)	20/33	13.6 (2)	
Pemetrexed (+)	14/23	18.72 (4.14)	0.47
Pemetrexed (-)	60/84	14.88 (2.24)	
Taxane (+)	55/75	14.88 (1.92)	0.58
Taxane (-)	19/32	17.00 (1.57)	
Platinum (+)	69/101	15.21 (1.92)	0.45
Platinum (-)	5/6	10.00 (4.69)	
Erlotinib (+)	13/18	21.52 (6.8)	0.15
Erlotinib (-)	61/89	14.8 (1.47)	
Vinorelbine (+)	15/20	17.47 (5.44)	0.68
Vinorelbine (-)	59/87	15.11 (1.53)	
Etoposide (+)	7/9	19.7 (2.9)	0.95
Etoposide (-)	67/98	15.11 (1.73)	

IHD (48.6 vs 9.7 %) and more likely to use RAS blockers (34.3 vs 8.3%) ($p < 0.01$ for all), as expected. The mean follow-up time was 17.8 months (range 1-102 months) for the all groups, 24.6 months (range 5-102 months) for the BB group and 14.5 months (range 1-92 months) for the C group. Of the 35 patients receiving BB during CT, 20 (57.1%) patients had a diagnosis of HT, 17 (48.6%) had IHD and 12 (34%) used a RAS blocker agent. Among the patients in the BB group, the most commonly prescribed BB agent was metoprolol (28/35, 80% of cases); other agents included carvedilol (3/35, 8.6%), atenolol (2/35, 5.7%) and nebivolol (2/35, 5.7%). At the time of the

Table 3. Multivariate Analysis of Overall Survival (OS)

Variables	HR	95%CI*	p
Beta-blocker: yes vs. no	0.69	0.36-1.34	0.27
Age: >60 vs. ≤60	1.13	0.69-1.86	0.61
Gender: female vs. male	0.82	0.28-2.39	0.72
ECOG: 2-3 vs. 0-1	0.92	0.42-2.02	0.85
Smoking: yes vs. no	1.04	0.44-2.46	0.92
Subtype: squamous vs. non-squamous	1.40	0.84-2.35	0.19
COPD: yes vs. no	2.52	0.92-6.85	0.07
IHD: yes vs. no	0.91	0.47-1.76	0.78
HT: yes vs. no	0.77	0.39-1.52	0.45
Diabetes: yes vs. no	1.78	0.90-3.53	0.09
RAS blocker: yes vs. no	1.16	0.55-2.46	0.68
CCB: yes vs. no	1.70	0.60-4.80	0.31

*CI: Confidence interval

**Figure 1. Kaplan-Meier Curves According to Beta-Blocker Usage**

analysis, 74 (69%) of all patients [48 patients in the C group (66%) and 26 in the BB group (74%)] had died.

Univariate analyses

The median OS of the entire group was 15.21 (± 1.78) months (95%CI: 11.71-18.71). The Kaplan-Meier estimates of the OS according to BB use illustrated that BB use was associated with a significantly improved OS (Figure 1). The median OS was 19.25 (± 2.87) months (95%CI: 13.62-24.88) in the BB group and 13.20 (± 2.37) months (95%CI: 8.55-17.85) in the C group ($p = 0.017$). None of the other variables examined in the UVA revealed a significant impact on OS (Table 2).

Multivariate analyses

After adjusting for age, gender, performance status, histologic subtype, smoking status, presence of comorbidities (COPD, IHD, HT and DM) and the use of other anti-hypertensive agents (RAS blockers or CCBs), the benefit of BBs on survival disappeared (HR: 0.59, 95%CI: 0.29-1.17, $p = 0.13$) (Table 3). None of these parameters was significantly associated with OS, but DM and COPD tended to decrease the OS (HR: 1.93, 95%CI: 0.97-3.84, $p = 0.06$; HR: 2.56, 95%CI: 0.94-6.96, $p = 0.06$, respectively).

Discussion

Lung cancer is the leading cause of cancer deaths worldwide; 80-85% of lung cancer cases are non-small cell lung cancer (NSCLC), predominantly adenocarcinoma (Jemal et al., 2007). Unfortunately, NSCLC is highly

resistant to current cancer therapeutics, and the survival rate beyond two years is still discouraging (Jemal et al., 2007; Al-Wadei et al., 2012).

Epinephrine and norepinephrine, which are induced by stress, are also associated with chronic illnesses of cardiovascular, immune and cancerous etiologies over the long term (Wong et al., 2011). Recent studies have emphasized the importance of beta-adrenergic signaling on cancer growth (Schuller et al., 1999; Laag et al., 2006; Al-Wadei et al., 2012; Cole and Sood, 2012). Within the tumour microenvironment, beta-adrenergic receptors (AR) on tumor and stromal cells are activated by catecholamines from local sympathetic nerve fibers (norepinephrine) and the circulating blood (epinephrine). Beta-adrenergic signaling has an important role in the initiation and progression of cancer, affecting inflammation, angiogenesis, apoptosis, cell migration, DNA damage repair and the epithelial-mesenchymal transition (Cole and Sood, 2012). Another explanation for the association of beta-adrenergic signaling with cancer growth may be related to the immune system (Ben-Eliyahu et al., 2000). Norepinephrine and beta-AR signaling have strong stimulating effects on a number of cancer types, including cancers of the colon (Masur et al., 2001; Wong et al., 2007), prostate (Palm et al., 2006), ovary (Sood et al., 2006; Thaker et al., 2006), breast (Drell et al., 2003) and pancreas (Al-Wadei et al., 2009).

Smoking is a documented risk factor for NSCLC (Al-Wadei et al., 2012). Nicotine and its derivatives play important roles in the stimulation of NSCLC growth (Catassi et al., 2008; Al-Wadei et al., 2012). In this regard, nicotinic acetylcholine receptors (nAChRs), beta-ARs (Schuller et al., 1999) and the activation of the beta-adrenergic signaling cascade (Schuller et al., 1999; Laag et al., 2006) and the Akt pathway (Carlisle et al., 2007) are important, as shown in many animal studies (Schuller and Orloff, 1998; Schuller et al., 2000; West et al., 2004; Arredonda et al., 2006; Schuller, 2008; 2009). Nicotine causes a deficiency in GABA, an antagonist of beta-adrenergic signalling (Al-Wadei et al., 2012). nAChRs are important for the autocrine-proliferative network that facilitates the growth of neoplastic cells (Catassi et al., 2008; Al-Wadei et al., 2012). Regarding the intensity of the adrenergic and muscarinic cholinergic receptors in lung cancer tissue versus normal lung parenchyma, a study showed that beta-ARs were decreased, whereas muscarinic receptors were increased in pulmonary adenocarcinoma (Kondratenko et al., 1991). However, beta-ARs and muscarinic cholinergic receptors were both decreased compared with healthy tissues in another study (Morin et al., 1987). In addition, the number of alpha 1-adrenergic sites and the ratio of alpha 1/beta binding sites is markedly increased in human lung cancer parenchyma (Kondratenko et al., 1993).

Beta-adrenergic stimulation activates downstream effector molecules (adenylyl cyclase/cAMP/PKA/CREB) concomitant with the transactivation of related pathways (EGFR) that lead to pro-oncogenic signaling (Al-Wadei et al., 2012). In this regard, the transactivation of the EGFR pathway via beta-adrenergic signaling may be a regulatory mechanism in a subgroup of lung adenocarcinomas among

smokers (Schuller and Cekanova, 2005).

In a recent study, the cooperation of nAChRs and beta-ARs has been identified as a stimulator of cancer development in NSCLC cell lines (Al-Wadei et al., 2012). NSCLC cells release their own stimulatory (noradrenaline) and inhibitory (GABA) neurotransmitters in response to nicotine. The effects of nAChRs can be reversed by the non-selective BB propranolol (Al-Wadei et al., 2012). Nicotine-induced NSCLC can be prevented by propranolol in hamsters, in which epinephrine had strong tumor-promoting effects (Schuller et al., 2000). In addition, animal studies demonstrated that both catecholamine and cAMP levels were elevated in nicotine-induced NSCLCs (Al-Wadei and Schuller, 2009; Al-Wadei et al., 2012) and that NSCLC growth could be reversed by atenolol (a cardioselective BB) (Schuller and Cekanova, 2005; Laag et al., 2006) or the inhibition of cAMP signaling (Al-Wadei et al., 2012).

Because cardiovascular diseases are common in the population, cancer patients frequently receive cardiovascular medications, including BBs. BBs have a demonstrated survival benefit in patients with hypertension, heart failure and coronary artery disease (Salpeter et al., 2002). The impact of concurrent cardiovascular medication on survival during cancer treatment has not been studied. Although there are some preclinical data (Schuller and Cekanova, 2005; Laag et al., 2006; Al-Wadei et al., 2012) that suggest the benefit of BBs in NSCLC, those studies were usually about preventing metastasis rather than the survival effect after metastasis. There are no clinical data showing that BBs are beneficial in metastatic NSCLC, and thus, we enrolled only metastatic patients in this study. We aimed to assess whether the use of BBs have an impact on the survival of metastatic NSCLC patients. In the present study, the overall survival (OS) of patients with metastatic NSCLC was compared retrospectively according to the use of BBs (35 patients were treated with BBs, and 72 patients were not). We found that the use of BBs significantly improved the OS. In the univariate analysis (UVA), BBs provided a six month survival benefit, although this survival benefit disappeared in the multivariate analysis (MVA). To our knowledge, this study is the first showing that BBs are associated with a better OS when used by metastatic NSCLC patients during CT. Our findings are in accord with preclinical studies about the relationship between NSCLC and beta-adrenergic signalling.

Although patients in the BB group had higher rates of serious comorbidities (HT and IHD) and a larger proportion of the patients in the BB group had died at the time of these analyses, we observed a six month OS benefit in the BB group compared with the C group. In addition, the follow-up period of the C group was shorter than that of the BB group. If the follow-up period was longer, then the number of events (death) could increase and a more significant survival benefit could be observed in the BB group. Our group was small, which may also explain why the survival benefit of the BB disappeared in the MVA.

In our study, we focused on all-cause mortality rather than cancer-specific or cardiovascular mortality. We did not find any association between BB usage and

chemotherapeutic agents or other anti-hypertensive drugs. The survival benefit of BBs is most likely not related to other clinicopathologic variables.

Our results do not agree with the study of Shah et al. (2011), who suggested that patients who have solid tumors (including NSCLC) and also use BBs for HT did not have a survival benefit. Recently diagnosed cancer patients receiving BBs regularly (n=1406) were compared with patients receiving other anti-hypertensive medications (n=2056). The BBs had no effect on the survival of common cancers (pancreas, ovarian, prostate, lung, breast, renal, esophagus, stomach or colorectal cancer). Most of the patients were receiving atenolol (75%) and were followed-up for one year (87% of patients). The patients receiving BBs had no survival benefit, but patients with pancreas and prostate cancer had a slightly poorer survival (Shah et al., 2011). Although that study had a larger sample size (n=1406) than ours, significant clinical parameters potentially affecting survival, such as other medications, chemotherapeutics, disease stage, histological subtype and importantly common comorbidities (e.g., COPD, diabetes and IHD), were not recorded or included in the survival analyses.

A recent study showed that BBs reduce the development of metastasis and recurrences in breast cancer and improve cancer-specific survival (Powe et al., 2010). Patients with non-metastatic breast cancer (n=466) were enrolled, and the follow-up period was >10 years. These patients were divided into two groups: 43 patients using BBs (predominantly atenolol) and 49 using other anti-hypertensive drugs. Metastasis development and tumor recurrence were significantly decreased, and the disease-free interval was increased in the BB group compared with both the non-HT control group (n=374) and HT group that did not use BBs (n=49) (Powe et al., 2010). However, that study did not evaluate male patients, the survival effect after metastasis or the impact of metoprolol. In addition, other comorbidities and medications significant for survival were unknown.

Wang et al. (2013) retrospectively reviewed 722 patients with non-metastatic NSCLC who received definitive radiotherapy (RT) with or without concurrent CT (Wang et al., 2013). Patients who received BB therapy (n=155) were compared with controls who did not receive BB therapy before or during RT. The BB usage (predominantly metoprolol and atenolol) significantly improved the OS, disease-free survival and distant metastasis-free survival (Wang et al., 2013). However, that study was unable to comment on whether metastatic NSCLC patients could benefit from BBs.

Our study has some limitations. The study group was small but appropriately matched according to well-known prognostic factors. Because this study was retrospective, some data may be missing or incomplete, such as the timing, duration or doses of the BBs, but all data were obtained from the patients' medical charts, not from the prescription database. The type of BBs may be important for the survival benefit. In this study, four types of BBs were used. Among these drugs, the beta-1 selective blocker metoprolol was primarily used. In this regard, a survival

benefit may be attributable to metoprolol because there was an insufficient number of patients receiving the other BB types. Thus, stating that the survival benefit is valid for all BB types or elucidating whether the type of BB is important for survival is difficult. In addition, we do not know the duration of BB usage before the CT or whether that factor is important. Despite these limitations, the results are encouraging for further prospective randomized studies.

In conclusion, this analysis demonstrated that the use of BBs (as clinically indicated) during CT may be associated with the improved OS of patients with metastatic NSCLC. BBs may be an inexpensive, feasible and effective method to prolong the survival of metastatic NSCLC patients when used concurrently during CT or targeted therapy. The prognostic effects of BBs on metastatic NSCLC should be investigated in more comprehensive studies with larger datasets to evaluate the duration, timing or type of BBs and their influence on the survival of patients with metastatic NSCLC.

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