The analysis of incidental receipt of beta-blocker medicine and overall survival outcome among patients with inoperable NSCLC

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BACKGROUND: To estimate the probability of improving survival outcome in NSCLC patients by using beta-blocker drugs and non-operative cancer treatment simultaneously.

METHODS: We retrospectively reviewed the medical record of 1494 non-operative NSCLC patients who had received radiotherapy and chemotherapy in medical database of Hunan Cancer Hospital from 1994-2005, 111 patients survived till the follow-up date on May 2011 after the whole treatment. 80 patients orally taken beta-blocker drugs were verified. The COX proportional hazard mode was utilized to conjecture the potential improvement of prognosis of non-operative NSCLC patients by using beta-block medicine.

RESULTS: The Kaplan–Meier illustrate that the use of beta-blocker was associated with improved OS ($P < 0.05$). The results from Uni-variate by using Cox proportional hazards regression models of the influence of confounders on the survival outcome indicate that the patients who was using beta-blockers medicine have better OS than non beta-blocker takers ($P < 0.01$). Multivariate Cox proportional hazards regression analysis indicated that the use of beta-blocker medicine significantly decrease the risk of mortality of inoperable NSCLC (RR = 0.770, 95.0% CI: 0.603-0.983, P =0.036).

CONCLUSION: Our prediction model estimate the beta-blocker medicine might play a key roll of improving the OS of non-operative NSCLC patients.

INTRODUCTION:

The beta-blocker drugs were widely used by the people who has cardiovascular disease, especially in the older people. Non Small Cell Lung Cancer(NSCLC) is the kind of cancer which used to be appear mostly in range of 45-65 ages, almost all of the patients will continuously intake the cardiovascular medicine while they are under and after the cancer treatment.

Several retrospective studies had demonstrated the possible clinical effect of beta-blocker medicine in cancer treatment[1-4, 25]. The efficacy of beta-blockers such as propranolol was recently

reported against infantile capillary hemangiomas[5], vascular endothelial growth factor (VEGF) is produced by most tumor types and stimulates the growth of new blood vessels within a tumor where it plays a key role in the process of angiogenesis [6].

Despite improvements in conventional anti-cancer therapies such as radiotherapy, chemotherapy, surgery and target cancer therapy, the five-year survival for NSCLC patients remains poor[7], the major cause of death is metastasis in NSCLC. The object of this study is to estimate the beta-blocker medicine might prolong the OS of NSCLC patients.

PATIENTS AND METHODS

Study population

We retrospectively reviewed the medical record of 1494 non-operative NSCLC patients who had received radiotherapy and chemotherapy in medical database of Hunan Cancer Hospital from 1994-2005 and verified the complication and medication via the relatives of the patients by telephone or mails.

The inclusion criteria were as follows: (I) diagnosed and pathologically confirmed NSCLC, (II) receipt of radiotherapy and chemotherapy without surgery, (III) medication of beta-blockers before, during and after the entire treatment. Exclusion criteria included the following: (I) history or findings of significant valvular heart disease (i.e. more than a mild valvular insufficiency or stenosis), hyperthyroidism or hypothyroidism and dilated or hypertrophic cardiomyopathy; (II) atrial fibrillation; (III) pregnancy or lactation; and/or (IV) a major systemic illness such as Systemic lupus erythematosus. Written consent form was obtained from all patients before the study. The present study was approved by the Ethics Committee of the Hunan Cancer Hospital, Changsha, China.

Measurement and definition

The patient database contained detailed patient demographic data, the patient's status (smoking index, alcohol intake, gender, age, etc), TNM and clinical stage, Pathological type, comprehensive tumor details, RT data, chemotherapy data, outcome, and mortality data. The disease was re-staged in accordance with the seventh edition of the American Joint Committee of Cancer (AJCC) TNM staging system [8] and the tumor pathological types were determined according to the WHO`s NSCLC classification [9].

Clinical endpoint

A total of 1494 patients were contacted by telephone or mail for evaluation of new death events. The data set was completed by information obtained from relatives or the survivals till May 2011.

Our main points of interest was death of NSCLC cause, other death of non-NSCLC cause was excluded.

Statistics analysis

Differences in the distribution of baseline characteristics between individuals with censor and outcome groups were examined using Chi-square test for categorical variables and Student's t-test for continuous variables. Descriptive statistics are presented as percentages or mean values with standard deviations (SD). All P-values are two-sided and values of <0.05 were considered statistically significant. Kaplan–Meier time-to-event analyses were used for clinical outcomes. Cox proportional hazards regression models adjusted for potential confounders were used to study the relation between relative risk of death events and medication of beta-blocker at baseline. First, univariate Cox regression analyses were carried out to examine the association between each potential confounder and clinical outcomes. Potential confounders for outcomes included TNM,and clinical stage, alcohol volume, smoking, age, gender, blood pressure, etc. Second, we fitted separate univariable Cox regression models to evaluate the influence of each covariate in the strength of association between medication of beta-blocker and clinical outcomes. Estimates derived from Cox regressions are presented as hazard ratios and 95% confidence intervals (CI). Statistical analyses were performed using SPSS version 18.0.

RESULTS

Baseline characteristics of subjects were showed in Table 1. The entire sample included 1494 subjects, the mean age of patients group of beta-blocker user and non beta blocker user were 61.66±7.821 and 55.39±9.537($p < 0.05$) respectively, we figure that the older people might have higher incidence in cardiovascular disease and hypertension($p < 0.01$), so they have more chance to orally take the beta-blocker medicine. NSCLC is the 1st cancer in male and 2nd in female in china recently, although the incidence rate ratios of NSCLC between males and females were decreased during the last decades, our database was ranged from 1994 to 2005, so the difference of gender was reasonable($p < 0.05$). The squamous cell carcinoma was the most predominate pathological type at that time($p < 0.05$), according to the study[26], the relative frequency of adenocarcinoma was increased from 21.96% to 43.36% range from 2010 to 2012. There are no difference in smoking index, alcohol abuse, T/N/M stage, clinical stage and differentiation($p > 0.05$).

The Kaplan–Meier (Figure 1) illustrate that the use of beta-blocker was associated with improved OS ($P < 0.05$). The results from Uni-variate by using Cox proportional hazards regression models of the influence of confounders on the survival outcome indicate that the patients who was using beta-blockers medicine have better OS than non beta-blocker takers(Table 2). The N/M stage($P < 0.01$) and lower differentiation($P < 0.05$) were linked with worse OS. Multivariate Cox proportional hazards regression analysis (Table 3)controlling potential confounders was conducted to evaluate the association between the use of beta-blocker and survival time of clinical outcomes. In this study, not only were co-variates such as gender, age, PS score, smoking index, alcohol volume/duration and hypertension considered as potential confounders, but also considered risk factors of clinical significant such as T/N/M stage, clinical stage and pathological type and differentiation. Multiple analysis indicated that the use of beta-blocker medicine significantly decrease the risk of mortality of non-operative NSCLC (RR =

0.770, 95.0% CI: 0.603-0.983, P =0.036).

DISCUSSION

Lung cancer was the leading cause of cancer-related mortality around the world, Non-small-cell lung cancer (NSCLC) accounts for 85%–90% of lung cancers over the last two decades[10]. Lung cancer is still increasing both in incidence and mortality worldwide, around 70% of patients with NSCLC present with locally advanced or metastatic at the time of diagnosis. Despite of the improvement of treatment, including radiotherapy, chemotherapy and targeted therapy, the 5-years overall survival rate was remains poor[7]. In this study, we performed a retrospective, large-scale, following-up study in Chinese patients. The main finding was the NSCLC patients take beta-blocker drugs orally and received definitive non-operative cancer treatment simultaneously have better OS than non-takers.

Cancer was the pathological condition that could stimulate more angiogenic factors to drive the uncontrolled angiogenesis of tumor vessels with distinct immature vascular structures[20-21]. The VEGF pathway is playing a key role as therapeutic target in NSCLC[11], where VEGF has been established as an important pro-angiogenic growth factor expressed in various types of cancers[12-14]. Avastin(Bevacizumab) has been proven successful in increasing the cancer response and in prolonging the overall survival in patients with NSCLC[15-16], which reminds us that beta-blocker might has the similar clinical effect. In some clinical retrospective studies reveal the similar results in different type of cancers[1-4, 25].

Oral beta-blocker medicine has recently been shown to be the highly effective drugs and is utilised as the first-line treatment for infantile hemangiomas[17-18]. Some recent in vitro experiments demonstrate the several possible mechanisms, (1)beta-blocker significantly decreased the expression levels of the HIF-1α (hypoxia inducible factor) in urine, serum and hemangioma tissues, however, the over-expression of HIF-1α suppress the effect of beta-blocker on VEGF [17,19], (2) beta-blocker decreased VEGF levels via the down-regulation of the PI3K/Akt/eNOS/ VEGF pathway[18]. All of those were demonstrated that VEGF was validated as pro-angiogenic molecule in angiogenesis and beta-blocker medicine could down-regulate the expression of VEGF just like Avastin does.

In some studies, beta-adrenoceptor inhibitors could decrease cell proliferation in vitro[22] and reduce tumor growth in vivo[23-24] by reducing the stress hormones adrenaline and/or nor-adrenaline to relief the chronic stress of cancer patients. Unfortunately, there are still no randomize double-blind bench-bed study to verify it.

The N/M stage are significantly influence the survival time of NSCLC patients, which is easy to understand, more advanced condition of cancer patients means more mortality rate.

Finally, we don`t have any further information of other complication or medicine combination of NSCLC patients in the database due to the limitation of the handwriting medical record, most of patients had not received concurrent radiotherapy and chemotherapy and the technology of radiation was 2D radiotherapy at that time in our hospital, all of those might confound our results.

CONCLUSION

In conclusion, our findings provide evidence that NSCLC patients who orally took the beta-

blocker medicine and received the non-operative cancer treatment simultaneously had better OS than the patients who had not used the drugs. Unfortunately, the mechanism is still unclear, we hypothesize the VEGF suppressing is the major cause. However, future prospective randomize double-blind clinical trials and more laboratorial research are needed to validate these findings.

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Table 1 Baseline characteristics of subjects

Characteristic	No. of patients/Mean±SD		P value
	Beta-blockers(N=80)	No beta-blockers(N=1414)	
Gender			<0.01
Male	57	1269	
Female	23	145	
Age	61.66±7.821	55.39±9.537	0.029
PS score			0.498
1	80	1412	
2	0	2	
Smoking index	541.38±627.435	566.34±499.271	0.668
Alcohol volume	0.42±1.527	0.56±2.37	0.586
Alcohol duration	61.66±7.821	55.39±9.537	0.858
Hypertension			<0.01
Yes	53	273	
No	27	1141	
T stage			0.968
T0	0	4	
T1	3	59	
T2	46	765	
T3	18	347	
T4	13	243	
N stage			0.728
N0	19	252	
N1	16	318	
N2	29	536	
N3	15	303	
M stage			0.988
M0	56	979	
M1	24	434	
Clinical stage			0.896
I	3	50	
II	17	248	
III	36	673	
IV	23	435	
Pathological type			0.019
Adeno	28	310	
Squamous	50	1032	
Other	2	72	
Differentiation			0.605
G1	5	98	

G2	27	549
G3	28	478
G4	17	250
Unidentified	2	14

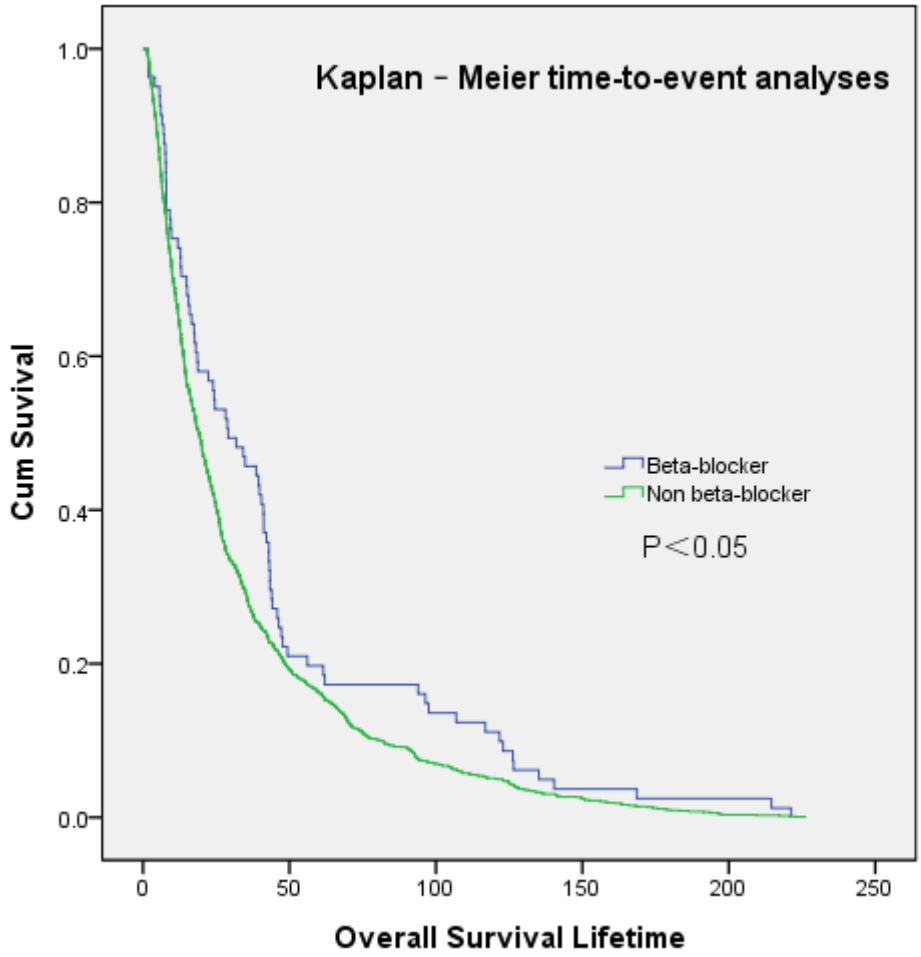

Table 2: Uni-variate survival analysis

Variable	Overall Survival Lifetime		P value
	HR	95%CI	
Gender	0.858	0.714-1.031	0.102
Age	1.005	0.999-1.011	0.133
PS score	2.008	0.490-8.225	0.332
Smoking index	1.000	1.000-1.000	0.430
Alcohol volume	0.995	0.968-1.022	0.689
Alcohol duration	1.001	0.993-1.009	0.811
Hypertension	1.085	0.976-1.206	0.130
Beta-blockers	0.698	0.537-0.909	0.008
T stage	1.033	0.966-1.105	0.345
N stage	1.132	1.064-1.205	< 0.01
M stage	1.525	1.276-1.822	< 0.01
Clinical stage	1.047	0.933-1.174	0.438
Pathological type	0.996	0.929-1.068	0.902
Differentiation	1.050	1.002-1.100	0.040

Table 2: Uni-variate survival analysis

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Gender	-.153	.094	2.670	1	.102	.858	.714	1.031
Age	.005	.003	2.260	1	.133	1.005	.999	1.011
PS score	.697	.719	.940	1	.332	2.008	.490	8.225
Smoking_index	.000	.000	.622	1	.430	1.000	1.000	1.000
Alcohol_volume	-.006	.014	.160	1	.689	.995	.968	1.022
Alcohol_duration	.001	.004	.057	1	.811	1.001	.993	1.009
Hypertension	.082	.054	2.294	1	.130	1.085	.976	1.206
β_blocker	-.359	.134	7.140	1	.008	.698	.537	.909
T_stage	.033	.035	.893	1	.345	1.033	.966	1.105
N_stage	.124	.032	15.233	1	.000	1.132	1.064	1.205
M_stage	.422	.091	21.480	1	.000	1.525	1.276	1.822
Clinical_stage	.046	.059	.602	1	.438	1.047	.933	1.174
Pathological_type	-.004	.036	.015	1	.902	.996	.929	1.068
Differentiation	.049	.024	4.232	1	.040	1.050	1.002	1.100

Table 3: Multivariate survival analysis

		B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for	
								Lower	Upper
Step 1	Gender	-.143	.093	2.379	1	.123	.867	.722	1.039
	Age	.005	.003	2.272	1	.132	1.005	.999	1.011
	Smoking_index	.000	.000	.780	1	.377	1.000	1.000	1.000
	Alcohol_volume	-.006	.014	.164	1	.686	.994	.968	1.022
	Alcohol_duration	.001	.004	.053	1	.818	1.001	.993	1.009
	Hypertension	.081	.054	2.266	1	.132	1.085	.976	1.206
	β_blocker	-.361	.134	7.203	1	.007	.697	.536	.907
	T_stage	.033	.034	.907	1	.341	1.033	.966	1.106
	N_stage	.124	.032	15.217	1	.000	1.132	1.064	1.205
	M_stage	.420	.091	21.294	1	.000	1.521	1.273	1.818
	Clinical_stage	.046	.059	.617	1	.432	1.047	.933	1.175
	Pathological_type	-.004	.036	.015	1	.901	.996	.929	1.067
	Differentiation	.049	.024	4.256	1	.039	1.050	1.002	1.100
Step 9	Gender	-.187	.088	4.512	1	.034	.829	.698	.986
	β_blocker	-.261	.125	4.410	1	.036	.770	.603	.983
	N_stage	.135	.028	23.485	1	.000	1.144	1.083	1.208
	M_stage	.473	.059	63.608	1	.000	1.605	1.429	1.803
	Differentiation	.051	.023	4.736	1	.030	1.052	1.005	1.102