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Original Article

Analysis of the effects of cyproheptadine on bladder cancer through big data

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Abstract: This study was designed to compare the efficacy of Cyproheptadine (CY) in patients with bladder cancer (BC) who received different therapeutic modalities. We used the database from a hospital in Taiwan for analysis. We included patients diagnosed as having bladder cancer from January 1, 2008, to December 31, 2017. The patient cohort comprised those who received different treatments, and we compared patients who received CY with those who did not. In total, 627 patients were included, and the mean follow-up duration was 3.26 years. All data were filtered out by 230 million data and 119 patients had used CY. Among them, 32 patients were used over 3 months of CY. The CY treatment curve shown by Kaplan-Meier survival curves for patients treated is higher than that of the non-CY effect. The value of Chi-squared statistic was 4.138 with associated *p*-value less than 0.05. Two survival curves shown by the result of the log rank test differ significantly. The grouping variable different treatments for non-CY and CY has a significant influence on survival rate. These results suggest that the use of CY may improve the survival rate of patients with BC.

Keywords: Cyproheptadine, bladder cancer, survival curves, big data

Introduction

Worldwide, urothelial carcinoma (UC) is the second-most common malignancy of the genitourinary tract and the 9th most common malignancy in Taiwan, causing approximately 1000 deaths annually. Bladder cancer is the 6th most common malignancy in the United States (US) [1]. Invasive UCs, despite treatment with radical surgery and adjuvant chemotherapy, remains with a poor 40% 5-year survival rate [2]. Bladder cancer begins when healthy cells in the bladder lining-most commonly urothelial cells-change and grow out of control, forming a mass called a tumor. Urothelial carcinoma (UC), also known as transitional cell carcinoma (TCC), is by far the most common type of bladder cancer. Other types of cancer can start in the bladder, but these are all much less common than urothelial (transitional cell) cancer. Urothelial cells also line other parts of the urinary tract, such as the part of the kidney that connects to the ureter (called the renal pelvis), the ureters, and the urethra. People with bladder cancer sometimes have tumors in these places, too, so all of the urinary tract needs to be checked for tumors. Bladder cancers are often described based on how far they have spread into the wall of the bladder: Non-invasive cancers are only in the inner layer of cells (the transitional epithelium). They have not grown into the deeper layers. Invasive cancers have grown into deeper layers of the bladder wall. These cancers are more likely to spread and are harder to treat [3]. Four types of standard treatments, such as surgery, radiation therapy, chemotherapy, and immunotherapy, are used [4]. Different types of treatment are available for patients with bladder cancer. Some treatments are standard (the currently used treatment), and some are being tested in clinical trials. A treatment clinical trial is a research study meant to help improve current treatments or obtain information on new treatments for patients with cancer. When clini-

cal trials show that a new treatment is better than the standard treatment, the new treatment may become the standard treatment [4]. Cyproheptadine (CY), an antihistamine, was initially approved in 1961 for allergic conditions but its use has been expanded to include treatment of serotonin syndrome, serotonin-induced sexual dysfunction, insomnia, headaches, and for use as an appetite stimulant. CY has been used for reducing all-cause deaths or deaths due to cancers in Taiwan [5]. CY is a first-generation anti-histamine, and it currently used to treat allergic reactions such as atopic dermatitis, anorexia, and migraines [6-8], and has been reported to be a novel therapeutic agent for treating multiple malignancies such as myeloma, leukemia and hepatocellular carcinoma (HCC) [9-11]. Other reported two advanced HCC cases with lung metastasis that experienced complete remission upon treatment with a combination of CY and thalidomide [10]. One patient, who is no longer receiving thalidomide but continues CY, remained tumor-free for > 22 months [10]. Other research results determined the effect of CY on the growth of five human UC cell lines and an in vivo xenograft model. The results showed that CY exerted an inhibitory effect on the proliferation of UC cells both in vitro and in vivo. CY also induced cell cycle arrest in the G1 phase, subsequently followed by apoptosis and necrosis [12]. Furthermore, CY induced apoptosis was associated with angiopoietin-like 4 (ANGPTL4) expression followed by activation of Caspase3 and poly ADP-ribose polymerase (PARP) in UC cells [12]. However, there were no large, prospective, randomized studies for comparison of the effectiveness in CY with those of different therapeutic modalities among BC patients. The time used for human experiment is longer and slower, so we assessed the therapeutic effects of CY on BC patients based on data analysis obtained from big data in this study.

Patients and methods

The Taiwan Cancer Registry Database was used for the analysis. Patients with BC who were treated from January 1, 2008, to December 31, 2017, were included in the study. Our protocols were reviewed and approved by the Institutional Review Board of Chiayi Christian Hospital (CYCH-IRB No. 2019051). All statistical analyses were conducted using SPSS software, Version 19. A two tailed *p* value of < 0.05 was considered significant. We categorized these patients into CY users and non-CY users. In this study, we filtered out 627 bladder cancer (BC) patients from more than 230 million medical records. Among these patients, 595 were non-CY users, and 32 of them used CY for more than 3 months. The defined daily dose (DDD), recommended by the World Health Organization (WHO), is a measurement of the prescribed drug amount. The DDD is the assumed average maintenance dose per day of a drug consumed for its main indication in adults [10]. Patients who received less than 3 months were defined as non-CY users. The possible confounding factors of comorbidities included age and sex. The primary endpoint of this study was the number of patient deaths during the study period. The cumulative incidence function of death was estimated using the Kaplan-Meier method [13]. Kaplan-Meier test is nonparametric in nature typically used for estimating the survival distribution, that is, to compute the fraction of participants who survived for a certain specified period after the intervention or treatment. It allows the estimation of survival over time even when the participants drop out or are studied for different time lengths. The estimator of the survival function $\hat{S}(t)$ (the probability that life is longer than t) is given by:

$$\hat{S}(t) = \prod_{i:\, t_i \leq t} \left(1 - \frac{d_i}{n_i}\right)$$

where $\hat{S}(t)$ is the estimated survival probability for any particular one of the *t* time periods; n_i is the number of subjects at risk at the beginning of time period t_i; and d_i is the number of subjects who die during time period t_i.

To describe how to evaluate whether or not Kaplan-Meier curves for two groups are statistically significant, log-rank test was used as the testing method. The log-rank test is a hypothesis test to compare the survival distribution of two samples. It is a nonparametric test and appropriate to use when the data are right skewed and censored. It is widely used in clinical trials to establish the efficacy of a new treatment in comparison with a control treatment when the measurement is the time to event [14]. A time-dependent Cox proportional hazard model was used to calculate hazard ratios (HRs) for death among patients with BC undergoing different treatment modalities with or without CY use. Kaplan-Meier estimate is one

Table 1. Baseline characteristics of patients with BC according to Cyproheptadine Status

	All (n=627)	Noncyproheptadine (n=595)	Cyproheptadine (n=32)	*p*-value
Age, years, mean (SD)	70.49 (12.02)	70.61 (12.06)	68.31 (11.15)	0.293
Median (Q1, Q3)	72 (62, 79)	72 (62, 80)	67.5 (63.25, 75.75)	
Min, max	21,97	21,97	42, 91	
20-44	10 (1.60)	9 (1.50)	1 (3.10)	
45-59	104 (16.60)	99 (16.60)	5 (15.60)	
60-74	255 (40.70)	239 (40.20)	16 (50.00)	
≥75	258 (41.10)	248 (41.70)	10 (31.30)	
Gender, n (%)				0.024
Male	442 (70.50)	426 (71.60)	16 (50.00)	
Female	185 (29.50)	169 (28.40)	16 (50.00)	
Follow-up years, mean (SD)	3.26 (2.80)	3.20 (2.79)	4.33 (2.90)	0.027
Median (Q1, Q3)	2.39 (0.91, 5.12)	2.33 (0.87, 5.01)	4.03 (1.64, 6.60)	
Min, max	0.01, 9.98	0.01, 9.98	0.15, 9.93	
Stage, n (%)				< 0.01
Stage I	405 (64.59)	386 (64.87)	19 (59.38)	
Stage II	95 (15.15)	88 (14.79)	7 (21.88)	
Stage III	65 (10.37)	63 (10.59)	2 (6.25)	
Stage IV	62 (9.89)	58 (9.25)	4 (12.50)	

Q1, Quartile 1; Q3, Quartile 3; SD, Standard Deviation.

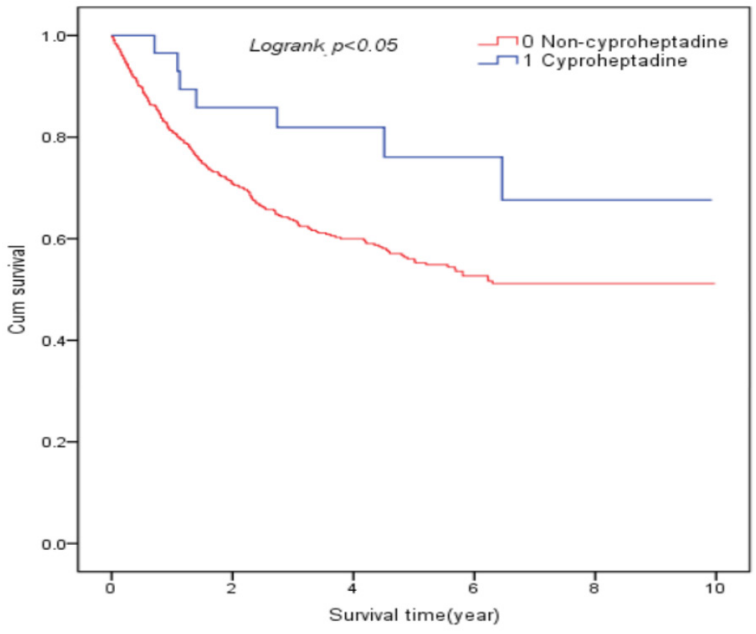

Figure 1. Kaplan-Meier survival curves for patients treated with Cyproheptadine users and non-Cyproheptadine users.

of the best options to be used to measure the fraction of subjects living for a certain amount of time after treatment. In clinical trials or community trials, the effect of an intervention is assessed by measuring the number of subjects survived or saved after that intervention over a period of time. The time starting from a defined point to the occurrence of a given event, for example death, is called as survival time and the analysis of group data as survival analysis [15].

Results

In total, we enrolled 627 patients of BC. The follow-up period is from the time the patients got bladder cancer until the end of the study. Because the survival time is different from patient to patient, the mean follow-up duration in this study was 3.26 years. Among these patients, 32 were CY users, and 595 were non-CY users. The mean age of the patients was higher and the follow-up duration was shorter in the non-CY user group than in the CY user group. Male patients even have a

Table 2. Comparison of survival curves (Log-rank test)

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	4.138	1	.042

Test of equality of survival distributions for the different levels of using Cyproheptadine for 3 months.

Table 3. Risk of deaths for patients with bladder cancer according gender and Cyproheptadine status

Risk factor	Regression coefficient	HR (95% CI)	*p*-Value
Noncyproheptadine VS Cyproheptadine			
Noncyproheptadine	0	1	
Cyproheptadine	-0.786	0.456 (0.214-0.970)	0.041*
Gender			
Male	0	1	
Female	-0.098	0.906 (0.685-1.199)	0.491

Cox regression. HR, Hazards Ratio. *$P < 0.05$.

two to three times higher risk of developing BC than female. Among the 595 non-CY users, 386 (64.87%) were BC Stage I patients, 88 (14.79%) were BC Stage II patients, 63 (10.59%) were BC Stage III patients and 58 (9.25%) were BC Stage IV patients. Among 32 CY users, 19 (59.38%) were BC Stage I patients, 7 (21.88%) were BC Stage II patients, 2 (6.25%) were BC Stage III patients and 4 (12.50%) were BC Stage IV patients (**Table 1**). Next we see the average survival time of the two groups. The median survival time of non-CY is 2.33 years; CY is 4.03 years. **Figure 1** shows Kaplan-Meier survival curves for patients treated with CY users and non-CY users.

Figure 1 contains two curves representing the follow-up of treatment with by CY and non-CY treatment, respectively. These are staircase curves with the corresponding margin for each event. The height of the margin is proportional to the number of events on the interval. The lost-of-view is represented by vertical bars throughout the staircase. These two survival curves are in the form of a staircase, continuous by piece and have jumped at each point of discontinuity. Finally, we note that the CY treatment curve is higher than that of the non-CY effect.

In **Table 2**, the data show the result of the log rank test for the comparison between the two survival curves. The Chi-squared statistic was 4.138 with associated *p*-value less than 0.05. The two survival curves differ significantly, the grouping variable has a significant influence on survival time. Hence the CY treatment is effective. A time-dependent Cox proportional hazard model was used to calculate hazard ratios (HRs) of deaths among patients for BC undergoing modalities with or without CY uses. In **Table 3**, risk of deaths for patients with bladder cancer is according to gender and CY status. The risk ratio of use CY compared to non-CY was 0.456, and $p < 0.05$ was statistically significant.

The stages (II-IV) of bladder cancer (BC) mean that cancer cells invade the connective tissue of the muscle wall, so we divide BC into two groups Stage I and Stage (II-IV). **Figure 2** shows Kaplan-Meier survival curves for patients of Stage I treated with CY users and non-CY users. **Figure 2** contains two curves representing the follow-up of treatments with Stage I by using CY and non-CY treatments. **Figure 3** shows Kaplan-Meier survival curves for patients of Stage (II-IV) treated with CY users and non-CY users. **Figure 3** contains two curves representing the follow-up of treatments with Stage (II-IV) by using CY and non- CY treatments. Finally, we note that the CY treatment curve is higher than that of the non-CY effect. In **Table 4**, by the data we can see the result of the log rank test for the comparison between the two survival curves. The Chi-squared statistic was 5.563 with associated *p*-value less than 0.05. The two survival curves differ significantly, and the grouping variable has a significant influence on survival time. Hence the CY treatment is effective.

Discussion

CY is a histamine and serotonin antagonist that has been observed to cause weight gain in observational studies of patients with advanced cancers. CY appears to be effective in patients with carcinoid syndrome who have anorexia or cachexia. In such patients, CY presumably acts by directly counteracting increased serotonin activity. CY, an inhibitor of the H1 histamine receptors, has recently shown activity in models of leukaemia and myeloma, presumably through inhibition of cyclin-D expression [16].

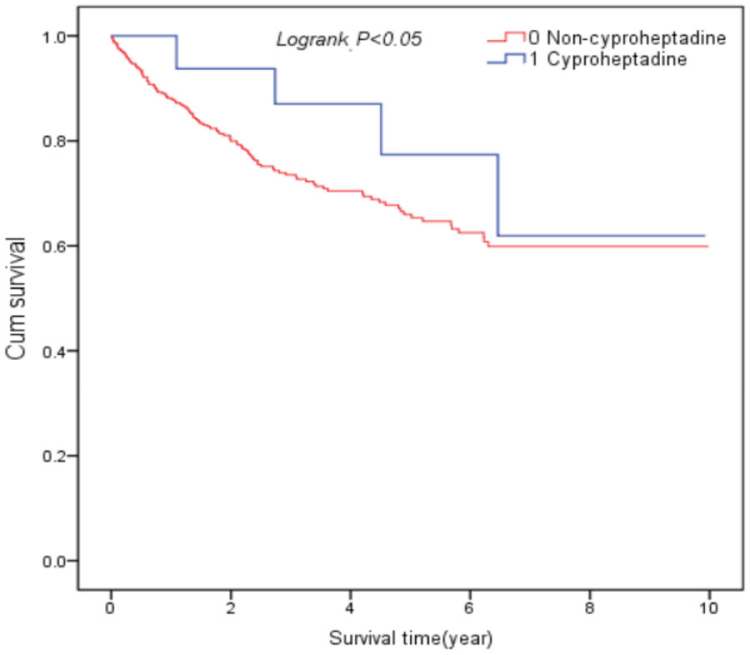

Figure 2. Kaplan-Meier survival curves for patients treated with Cyproheptadine users and non-Cyproheptadine users show bladder cancer Stage I.

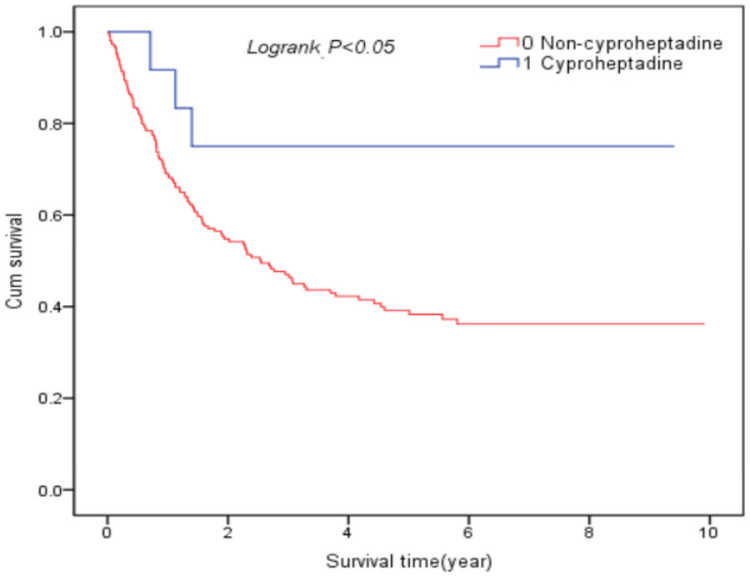

Figure 3. Kaplan-Meier survival curves for patients treated with Cyproheptadine users and non-Cyproheptadine users show bladder cancer Stage II-IV.

Table 4. Bladder cancer stage comparison of survival curves (Log-rank test)

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	5.563	1	.018

Test of equality of survival distributions for the different levels of using Cyproheptadine for 3 months (Adjusted for Stage I-IV).

CY use could induce apoptosis of residual HCC cells to improve survival [17]. Recently, CY showed an anticancer effect in various cancer cells such as human colon carcinoma cells (HT29), acute lymphoblastic leukemia cells, human breast cancer cells (MCF-7), and HCC (HepG2 and Huh-7) [18]. In this study, BC patients were filtered into 627 patients by using CY from 230 million data. Big data in healthcare is important as it can be used in the prediction of outcome of diseases prevention of co-morbidities, mortality and saving the cost of medical treatment. In many countries, big data has becoming an important database where information generated could be used for treatment and management of diseases. Our results indicating the use of CY for more than 3 months has a significant effect on bladder cancer. The risk ratio of using CY compared to non-CY was 0.456, and $p < 0.05$ was statistically significant. In addition, given that CY is inexpensive with a daily cost of US$0.2 in Taiwan, the addition of CY would not result in an additional financial burden for the patients [19]. However, this study was only a retrospective study. A prospective clinical trial with a larger sample size is needed for further investigation.

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Department of Medical Research, Ditmanson Medical Foundation Chiayi Christian Hospital.

Disclosure of conflict of interest

None.

Abbreviations

BC, Bladder cancer; UC, Urothelial carcinoma; CY, Cyproheptadine; DDD, Defined daily dose;

TCC, Transitional cell carcinoma; HRs, Hazard ratios; WHO, World Health Organization; HCC, Hepatocellular carcinoma.

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