



The Prophylactic Effect of Amiodarone on HCC Occurrence

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Editorial

Autophagy is catabolic process to maintain cellular homeostasis through its recycling machinery. Cytosolic long lived or aggregated proteins, micro RNAs and excess or defective organelles can be selectively or non-selectively recruited to the double membrane auto phago some, followed by fusion with the lysosome and degradation to recycle the degraded materials [1-4]. We previously demonstrated that amiodarone, a class III antiarrhythmic agent and a potent mTOR inhibitor [5], effectively suppressed liver tumor formation through induction of autophagic activity in the rat orthotopic model and in the mouse xenograft model [3,4]. Amiodarone is a FDA approved drug for various types of cardiac dysrhythmias [6]. Lin et al. reported that amiodarone reduces liver injury and promotes liver regeneration after partial hepatectomy through activation of Autophagy [7]. We demonstrated that the effective dose used to suppress liver tumor formation in rats (30 mg/kg) is equivalent to 4.8 mg/kg in a human adult based on Reagan-Shaw’s conversion formula, which is much lower than the dose used to treat antiarrhythmic disease (1,000 mg/kg). Despite amiodarone uptake might cause side effects on lung, thyroid, and liver [8,9], it has been used in clinical as a supportive adjuvant of the traditional anti-HCC drugs to increase survival rate and lifespan of the HCC patients who received Transcatheter Arterial Chemoembolization (TACE). Notably, amiodarone-treated patients showed no evident toxicity [10,11].

Furthermore, we conducted a big data analysis of 32,625 case-control provided by Taiwan’s National Health Insurance (NHI) program and reveal that long-term regular amiodarone usage significantly decreases the risk of Hepatocellular Carcinoma (HCC) occurrence, however, short-term exposure shows opposite effect (Table 1). Su et al., also claimed a borderline risk of HCC occurrence among users of amiodarone after analysis of the big data of NHI [12]. The discrepancy may be caused by the following possibilities: (1) they did not consider the patients’ comorbidities in the multivariate regression models. Differently, we included patients’ comorbidities in the multivariate analysis (Table 1); (2) they did not evaluate the cumulative effect of long-period usage of amiodarone. We classified the exposure length of amiodarone into <365, 365-730, and >730 Cumulative Defined Daily Doses (cDDD) groups and found that a reduced risk of HCC occurrence

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Received Date: 10 Sep 2018

Accepted Date: 30 Sep 2018

Published Date: 06 Oct 2018

Citation:

Wu S-Y, Liu H-S, Lan S-H. The Prophylactic Effect of Amiodarone on HCC Occurrence. Clin Oncol. 2018; 3: 1527.

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Table 1: Characteristics of Taiwan nationwide population-based claims data.

Variable	Control	Control (%)	Case	Case (%)	p-value
Age					1
0 ≤ age < 25	132	0.5	33	0.5	
25 ≤ age < 35	852	3.3	213	3.3	
35 ≤ age < 45	2632	10.1	658	10.1	
45 ≤ age < 55	4928	18.9	1232	18.9	
55 ≤ age < 65	6036	23.1	1509	23.1	
age ≥ 65	11520	44.1	2880	44.1	
Sex					1
Male	17212	65.9	4303	65.9	
Female	8888	34.1	2222	34.1	
CCI score	0.65 ± 1.15[†]		2.00 ± 2.35[†]		< 0.0001

CCI score: Charlson Comorbidity Index Score

[†]represent means ± SD

Table 2: Association between amiodarone use and risk of HCC occurrence.

Variable	Control	Control (%)	Case	Case (%)	Adjusted OR* (95% CI)	p-value
Overall						
Never used	25640	98.2	6340	97.2	1	
Ever used	460	1.8	185	2.8	0.78 (0.64-0.94)	0.011
Cumulative use						
≤ 365 cDDD	354	77	146	78.9	1	
365-730 cDDD	50	10.9	28	15.1	1.36 (0.82-2.24)	0.232
> 730 cDDD	56	12.2	11	6	0.48 (0.24-0.94)	0.031

*Multiple logistic regression, adjusting for patient's comorbidities.

cDDD: Cumulative Defined Daily Doses; OR: Odds Ratio; CI: Confidence Interval

was associated with the long-term usage group (Table 2). In addition, the low OR value and high margin of error of 95% CI in the long-term exposure of amiodarone (cDDD>730) group is related to the limited sample number (n=11). Further pharmaco-epidemiological study using a larger sample size is needed. Nevertheless, big-data analysis supports the suppressive role of amiodarone in HCC development. Altogether, our result simply that amiodarone as a repurposing drug has the potential to be used as a novel anti-tumor agent for HCC therapy.

Conclusion

Amiodarone as a repurposing drug has the anti-tumor activity to suppresses liver tumor formation and prevent HCC incidence through induction of the autophagic activity.

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