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The Role of beta-blockers in lung cancer treatment: An *in vitro* approach

Chaired by **DR. ALFREDO BERZAL-HERRANZ**; Co-Chaired by **PROF. DR. MARIA EMÍLIA SOUSA**





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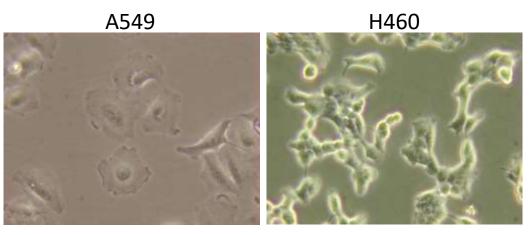


The Role of beta-blockers in lung cancer treatment: An in vitro approach

Singular exposure

Drugs used:

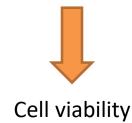
- Propranolol
- Carvedilol
- Cisplatin
- Etoposide



Combined Exposures

Mixtures used:

- Propranolol + Cisplatin
- Propranolol + Etoposide
- Cisplatin Etoposide





Abstract: In 2020, lung cancer was the second most common type of cancer in the world and the most lethal. Due to the high mortality rate and the low efficiency of available treatments, there is the need for more efficient approaches to fight this disease. In this regard, the use of already approved pharmaceuticals for other purposes can be valuable. Thus, the study aimed to assess the potential application of β-blockers, alone or combined with cytostatic drugs. The effects of the β-blockers propranolol (10, 25, 50, 100, 125, 150, 200 and 250 μM) and carvedilol (0.1, 1, 5, 10, 20, 60, 75 and 100 μM) and cytostatic drugs cisplatin (1, 5, 20, 50, 100, 150, 200, and 250 μM) and etoposide (0.005, 0.1, 0.5, 1, 2.5, 5, 7.5 and 10 μM) were evaluated in cancer cell lines, A549 and H460, at different time points (24, 48 and 72h), through cell viability. Overall, A549 demonstrated higher sensitivity to propranolol, cisplatin, and etoposide and H460 was more sensitive to carvedilol. The study of combined effects of β-blockers and cytostatic drugs revealed the potential value of β-blockers in the treatment of cancer.

Keywords: β-Blockers, Lung Cancer, Cell Viability, Cytostatic, Cell Lines

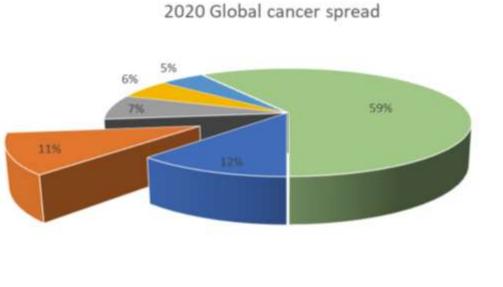


Causes:

- UV radiation
- Tabaco
- Pharmacology
- Parasites
- Bacteria
- Fungi

Treatments:

- Surgery
- Chemotherapy
- Radiation therapy
- Targeted therapy





High mortality rates and low efficiency of the available treatments highlight the need for a new approaches



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Lung Cancer

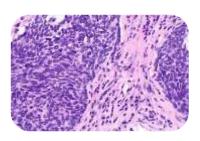
Chest Wall Tumours



Mesothelioma



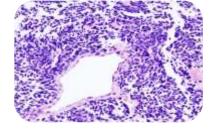
Non-Small Cell Lung Cancer



Lung nodules



Small Cell Lung Cancer

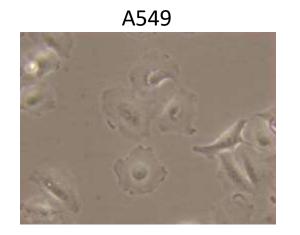


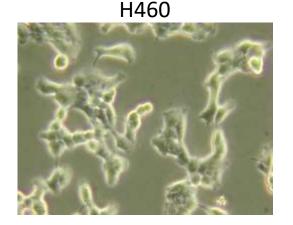




β-Adrenergic Cytostatic Drugs Receptors β2 β1 Used for cancer treatment Tested pharmaceuticals: Commonly used in Prevent cell replication or Cisplatin Propranolol abnormal heart rhythms. growth. Carvedilol **Etoposide**





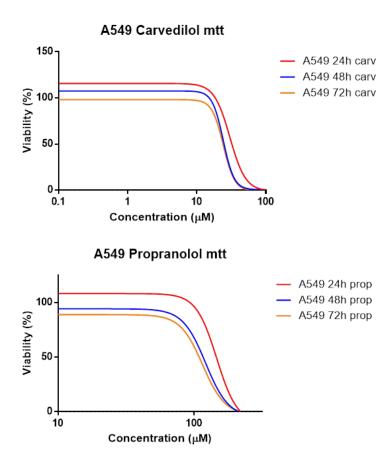


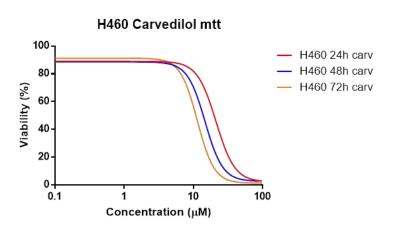
The cytotoxicity of **non-selective** β-**blockers** (carvedilol and propranolol), and **cytostatic drugs** (cisplatin and etoposide), was assessed **on lung cancer cell lines**A549 and H460

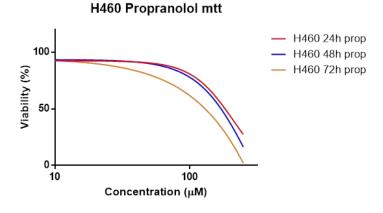
Effects of **binary combinations** of Propranolol with Cisplatin, Propranolol with Etoposide and Etoposide with Cisplatin were tested



Results: beta-blockers









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Results and discussion:

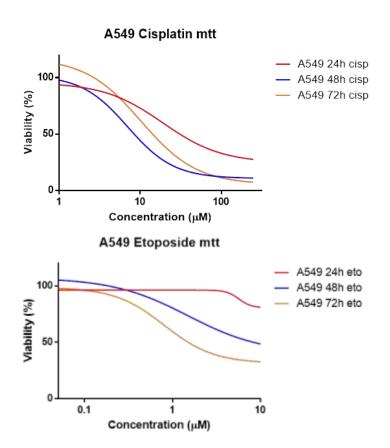
Table of LD₅₀ and LD₂₅: Carvedilol

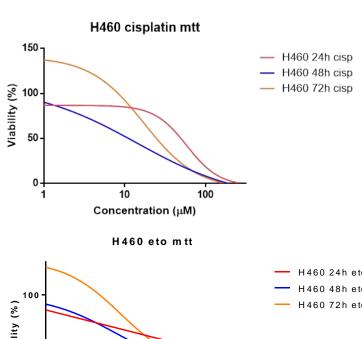
Carvedilol	μМ	24 h	48 h	72 h
A459	LD ₅₀	33.065	25.262	24.070
	LD ₂₅	25.798	20.447	19.732
H460	LD ₅₀	19.164	13.861	10.860
	LD ₂₅	11.528	8.994	7.4255

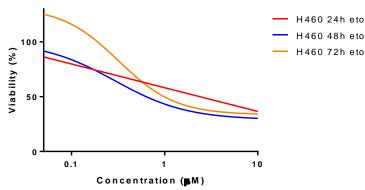
Table of LD₅₀ and LD₂₅: Propranolol

Propranolol	μΜ	24 h	48 h	72 h
A459	LD ₅₀	145.560	116.446	108.942
	LD ₂₅	124.294	92.236	83.476
H460	LD ₅₀	171.623	149.218	126.553
	LD ₂₅	108.645	71.647	62.901

Results: cytostatic drugs









Results and discussion:

Table of LD₅₀ and LD₂₅: Cisplatin

Cisplatin	μМ	24 h	48 h	72 h
A459	LD ₅₀	30.886	8.447	14.243
	LD ₂₅	8.960	3.990	6.930
H460	LD ₅₀	49.723	11.197	24.766
	LD ₂₅	24.648	3.072	14.654

Table of LD₅₀ and LD₂₅: Etoposide

Etoposide	μМ	24 h	48 h	72 h
A459	LD ₅₀		8.368	1.506
	LD ₂₅		1.383	0.546
H460	LD ₅₀	2.252	0.474	0.747
	LD ₂₅	0.168	0.116	0.313

Results and discussion: Effects of Combined Exposures on A549



Etoposide + Propranolol

8.45	54,302	58,456	51,725	46,589	36,287
6.34	67,509	57,767	59,158	45,649	38,016
4.22	73,130	65,044	63,354	52,556	41,649
2.11	80,445	71,854	79,866	69,076	39,715
0	100,000	97,844	88,056	81,531	55,242
	0	29.11	58.22	87.33	116.45
	6.34 4.22 2.11	6.34 67,509 4.22 73,130 2.11 80,445 0 100,000	6.34 67,509 57,767 4.22 73,130 65,044 2.11 80,445 71,854 0 100,000 97,844	6.34 67,509 57,767 59,158 4.22 73,130 65,044 63,354 2.11 80,445 71,854 79,866 0 100,000 97,844 88,056	6.34 67,509 57,767 59,158 45,649 4.22 73,130 65,044 63,354 52,556 2.11 80,445 71,854 79,866 69,076 0 100,000 97,844 88,056 81,531

ய		0	29.11	58.22	87.33	116.45
top	0	100,000	121,120	86,930	60,073	26,188
Etoposide	2.09	80,356	82,554	59,104	43,148	25,855
	4.18	68,466	72,890	51,918	50,658	25,189
(mM)	6.28	70,997	70,574	60,069	47,098	37,577
	8.37	68,549	55,512	46,926	44,208	32,895

Propranolol (µM)

Propranolol (µM)

Cell viability
100-80
80-60
60-40
40-20
20-0

Cisplatin + Etoposide

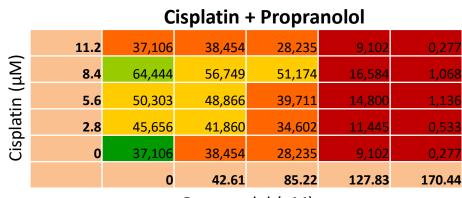
		0	2.11	4.22	6.34	8.45
Cisplatin	0	100,000	82,565	74,080	65,972	54,759
lati	2.09	83,890	75,284	69,961	63,355	55,985
	4.18	75,572	62,430	65,345	54,631	54,228
(MM)	6.28	58,624	67,637	58,544	51,048	54,695
	8.37	62,545	60,059	63,122	49,587	48,094

Etoposide (µM)

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Results and discussion: Effects of Combined Exposures on H460



Etoposide + Propranolol

=	0.47	19,305	28,357	20,489	5,105	1,672
(MH)	0.36	18,646	23,943	23,095	5,326	1,448
	0.24	19,557	24,264	24,941	6,963	1,740
Etoposide	0.12	25,590	30,751	29,565	8,949	1,935
Etop	0	100,000	82,770	73,798	29,334	3,001
		0	42.61	85.22	127.83	170.44

Propranolol (μM)

Propranolol (μM)

Cell viability
100-80
80-60
60-40
40-20
20-0

Cisplatin + Etoposide

		0	2.8	5.6	8.4	11.2
Cisplatin	0	100,000	67,898	47,506	32,929	35,976
olati	0.12	29,446	24,137	23,815	18,263	24,446
<u>)</u> u	0.24	24,195	22,450	19,489	22,576	20,734
(mm)	0.36	23,252	18,998	17,637	22,385	20,424
	0.47	22,819	21,143	16,432	20,740	19,838

Etoposide (µM)



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Conclusions

Cytostatic drugs showed higher toxicity than the β-blockers to the cell lines in study;

Propranolol, Carvedilol and Cisplatin cytotoxicity increased in a concentration dependent manner;

Etoposide cytotoxicity increased in a time dependent way in A549;

A549 was more resistant to carvedilol and etoposide while H460 to cisplatin and propranolol;

The binary mixtures showed that Propranolol combined with Etoposide and Cisplatin demonstrated a synergistic effect culminating in higher cell death;

For a future reference Human bronchial epithelial cells: HBEpC could also be used to test the effects on a non cancerous cell line.



Acknowledgments

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