Non-selective beta-blockers as potential coadjutants for prostate cancer treatment

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Non-selective beta-blockers as potential coadjuvants for prostate cancer treatment

**Pharmaceutical Alone**
- Propranolol
- Carvedilol
- Atenolol
- Metoprolol
- Cisplatin
- Flutamide

**Combined Exposure**
- Propranolol + Cisplatin
- Propranolol + Flutamide

**Different Cells Lines**
- 22Rv1
- LNCaP
- PC3
- PNT-2

**Effects**
- Cell Viability
Abstract: Prostate cancer is the third most diagnosed cancer worldwide, and the second cause of cancer death in men. The treatments currently available are not always effective. For that reason, new treatment options need to be explored, which can include the use of drugs, already clinically available, used for the treatment of other conditions, such as β-blockers. The present study aimed to explore the effects of several β-blockers and cytostatic drugs in prostate cancer cell lines (22Rv1, LNCaP and PC3) and a normal prostate cell line (PNT-2). Cells were exposed up to 72 h to increasing concentrations of propranolol, carvedilol (both non-selective β-blockers), atenolol, metoprolol (both β1-blockers), cisplatin (a cytostatic drug) and flutamide (an androgen receptor blocker) and cell viability was assessed. The non-selective β-blockers selected, propranolol and carvedilol and cytostatic drugs displayed cytotoxic effect on all cell lines, while the β1-blockers, metoprolol and atenolol did not alter significantly cells viability. Of the tested cell lines, 22Rv1 was the most sensitive to propranolol, carvedilol and cisplatin and PC3 was the most resistant. Therefore, sensitive line 22Rv1, resistant line PC3 and normal cell line PNT-2 were chosen for combined treatment between propranolol and cytostatic cisplatin and flutamide. Overall, the combined exposures revealed concentration dependent interactions between the cytostatic drugs and propranolol.

Keywords: beta-blockers, cancer cell lines, cell viability, combined treatments
Introduction

Available Treatments for Prostate Cancer:
- Active Surveillance
- Radical Prostatectomy
- Radiation Therapy
- Focal Therapy
- Hormone Therapy
- Chemotherapy
- Immunotherapy
- Nanotherapeutics

Limited Efficiency
Specially in advanced disease

β-Blockers  New Approaches

Percentage of new cases of cancer in 2020, both sexes, worldwide

- 11.70% Breast
- 11.40% Lung
- 7.30% Prostate
- 6.00% Colon
- 5.60% Stomach
- 58.00% Other Cancers

Global Cancer Observatory of 2020
Introduction

β-Adrenergic Signalling

“Fight-or-flight” stress response

Catecholamines

Related to:
Angiogenesis
Migration
Metastasis

β-Adrenergic Receptors

β1

Can be found in:
Heart
Peripheral sympathetic nerves
Kidney
Vascular

β1-Blockers (e.g., Atenolol, Metoprolol)

β2

Can be found in:
Heart
Lung
Peripheral sympathetic nerves
Vascular
Principal isoform in Prostate Cancer

β3

Can be found in:
Adipocytes
Heart
Colon
Peripheral sympathetic nerves
Vascular

Non selective β-Blockers (e.g., Carvedilol, Propranolol)
Introduction

In this study:

The cytotoxicity of $\beta_1$-blockers (atenolol and metoprolol), non-selective $\beta$-blockers (carvedilol and propranolol), and cytostatic drugs (cisplatin and flutamide), was assessed on prostate cancer cell lines (22Rv1, LNCaP and PC3) and on a normal prostate cell line (PNT-2).

Effects of binary combinations of propranolol with cisplatin and propranolol with flutamide, were assessed on PNT-2, 22Rv1 and PC3 cells.
Results and Discussion

Atenolol induced small reduction of cell viability in a time and concentration dependent manner.

*test media renewal at every 24 h

Atenolol induced small reduction of cell viability in a time and concentration dependent manner.
Results and Discussion

Atenolol

Atenolol induced small reduction of cell viability in a time and concentration dependent manner.

*test media renewal at every 24 h

LNCaP

PC3
Results and Discussion

Metoprolol

PNT -2 – Normal Cell line

22Rv1

Metoprolol induced small reduction of cell viability in a time and concentration dependent manner
Results and Discussion

Metoprolol

Metoprolol induced small reduction of cell viability in a time and concentration dependent manner.

LNCaP

PC3

*test media renewal at every 24 h
Results and Discussion

Carvedilol

PNT -2 – Normal Cell line

22Rv1

Carvedilol showed time and concentration dependent cytotoxicity

*test media renewal at every 24 h
Results and Discussion

Carvedilol

Carvedilol showed time and concentration dependent cytotoxicity

*test media renewal at every 24 h
Results and Discussion

Propranolol

Propranolol showed time and concentration dependent cytotoxicity

*test media renewal at every 24 h

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01-30 November 2021 | Online
Results and Discussion

Propranolol showed time and concentration dependent cytotoxicity
### Results and Discussion

<table>
<thead>
<tr>
<th>72 h LD$_{50}$ (µM)</th>
<th>Carvedilol</th>
<th>Propranolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNT-2</td>
<td>17.211</td>
<td>108.953</td>
</tr>
<tr>
<td><strong>22Rv1</strong></td>
<td><strong>14.990</strong></td>
<td><strong>54.639</strong></td>
</tr>
<tr>
<td>LNCaP</td>
<td>27.328</td>
<td>64.366</td>
</tr>
<tr>
<td><strong>PC3</strong></td>
<td><strong>31.368</strong></td>
<td><strong>183.899</strong></td>
</tr>
</tbody>
</table>

22Rv1 was the most sensitive cell line and PC3 was the most resistant.
Results and Discussion

Cisplatin

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>24 h</th>
<th>48 h</th>
<th>48 h with Change*</th>
<th>72 h</th>
<th>72 h with Change*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNT-2</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>22Rv1</td>
<td>147.568</td>
<td>212.775</td>
<td>214.681</td>
<td>72 h</td>
<td>72 h with Change*</td>
</tr>
<tr>
<td>LNCaP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC3</td>
<td></td>
<td></td>
<td></td>
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</table>

*test media renewal at every 24 h
Results and Discussion

Flutamide

<table>
<thead>
<tr>
<th>Flutamide</th>
<th>PNT-2</th>
<th>22Rv1</th>
<th>LNCaP</th>
<th>PC3</th>
</tr>
</thead>
<tbody>
<tr>
<td>72 h LD&lt;sub&gt;50&lt;/sub&gt; (μM)</td>
<td>------</td>
<td>248,645</td>
<td>220,067</td>
<td>275,430</td>
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</table>

*test media renewal at every 24 h
Results and Discussion

Combined Exposure – Propranolol and Cisplatin

MixTox Model
Dose ratio-dependent deviation

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<tr>
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<th>Value</th>
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</thead>
<tbody>
<tr>
<td>a</td>
<td>2.149485</td>
</tr>
<tr>
<td>b</td>
<td>-3.829912</td>
</tr>
</tbody>
</table>

- $a > 0$ Antagonism at lower concentrations of propranolol
- $b < 0$ Synergism at higher concentrations of propranolol
Results and Discussion

Combined Exposure – Propranolol and Cisplatin

MixTox Model
Dose level-dependent deviation

<p>| | |</p>
<table>
<thead>
<tr>
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<th></th>
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<tbody>
<tr>
<td>a</td>
<td>-2.2778721</td>
</tr>
<tr>
<td>b</td>
<td>2.1004136</td>
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</tbody>
</table>

a < 0  Synergism at lower concentrations of propranolol

b > 0  Antagonism at higher concentrations of propranolol
Results and Discussion

MixTox Model
Independent Action

Antagonism
Conclusions

Non-selective β-Blockers (carvedilol and propranolol) showed higher cytotoxic effects than β1-Blockers (atenolol and metoprolol) in all cell lines.

Non-selective β-Blockers, β1-Blockers, Cisplatin and Flutamide cytotoxicity increased in a time-dependent manner.

22Rv1 was the most sensitive cell line to carvedilol, propranolol and cisplatin and PC3 the most resistant cell line.

The binary mixtures showed that at lower concentrations propranolol has a protective effect on PNT-2 (normal cell line), while for the same concentrations, the cytotoxic effects of cisplatin to the prostate cancer cell 22Rv1 was increased.

Data suggest the potential role of propranolol on cancer treatment.
Acknowledgments

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