Cytoselective anticancer properties of copper-based metal complexes against nasopharyngeal carcinoma

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INTRODUCTION

Nasopharyngeal cancer (NPC) is a major head and neck cancer in a number of developing countries in Northern Africa and Asia, including Malaysia. The treatment of choice for this cancer is chemoradiotherapy. The platinum-based drug, cisplatin is the main chemotherapeutic agent used. Treatment of refractory cases remains a significant problem. We sought to test whether copper complexes based on Cu(II) complexes which are relatively stable at room temperature and economical to synthesize, are effective against NPC cells and could be developed as an alternative to platinum-based drugs.

OBJECTIVES

The purpose of the study was to test the efficacy of copper ternary complexes, [Cu(phen)(aa)(H2O)]NO3·xH2O, against NPC and other cancer cells, and to determine the molecular mechanisms underlying the anticancer properties.

RESULTS

1. Characterization of [Cu(phen)(aa)(H2O)]NO3 complexes

The positive-ion ESI mass spectrum of methanolic solution of the copper complex. The positive-ion mass spectrum shows two intense Cu(phen)(aa)(H2O) peaks due to the different isotope Cu(63) and Cu(65) with the correct isotope distribution.

2. [Cu(phen)(aa)(H2O)]NO3 complexes display significantly greater cytotoxic effects against cancer cells compared to non-malignant cells

Table 1. IC50 values of [Cu(phen)(aa)(H2O)]NO3·xH2O (1–4) and Cu(phen)NO3 for HK1 NPC cells vs non-malignant NPEP nasopharyngeal epithelial cells

<table>
<thead>
<tr>
<th>Compound</th>
<th>HK1 NPC</th>
<th>NPEP</th>
<th>HK1 NPC</th>
<th>NPEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Cu(phen)(aa)(H2O)]NO3</td>
<td>47.2 μM</td>
<td>1.8 μM</td>
<td>47.2 μM</td>
<td>1.8 μM</td>
</tr>
<tr>
<td>Cu(phen)NO3</td>
<td>85.7 μM</td>
<td>3.7 μM</td>
<td>85.7 μM</td>
<td>3.7 μM</td>
</tr>
</tbody>
</table>

DISCUSSION AND CONCLUSIONS

The synthesized [Cu(phen)(aa)(H2O)]NO3 complexes were characterized. The complexes showed IC50 values between 2.2 – 5.2 μM against NPC HK1 cells while the corresponding values for nasopharyngeal epithelial non-cancerous (NPEP) cells were greater than 13.0 μM. At 5 μM, the complexes induced 41 – 60% apoptotic cell death in NPC cells. This was significantly greater than the effects of the complexes on NPEP cells. In contrast, neither copper complexes, Cu(phen)NO3, induced apoptosis in over 80% of NPC and NPEP cells. Proteasome inhibition were tested on stably transduced HK1 expressing Ubb-GST-GFP shows increased of fluorescence at 9 hours. The treatment also inhibited Topoisomerase I. Cu(phen)(aa)(H2O)]NO3 complexes was also be found to be effective against other NPC cells (C666-1 and HONE-1) as well as cervical, lung, breast, lymphoma, leukemia, and colorectal cancer cells. The US National Cancer Institute (NCI) 60 human tumour cell line anticancer drug screen (NCI60) showed that the complex was cytotoxic to a wide variety of cancer cell types. Preliminary preclinical studies in mice suggested that the copper complex, at a dose which could inhibit tumour growth, did not result in significant toxicity as shown in body weight. Taken together, our data suggests that the [Cu(phen)(aa)(H2O)]NO3 complexes could potentially be useful as anti-cancer agents.

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REFERENCES

