Targeting αvβ6-integrins using micellar nanoparticles for delivery of PNKP inhibitors to non-small cell lung cancer (NSCLC)

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INTRODUCTION

The inhibition of polynucleotide kinase/phosphate (PNKP), an enzyme involved in DNA repair, simultaneously with the disruption of phosphatase and tensin homologue (PTEN) has been shown to cause synthetic lethality in cancer cells. In non-small lung cancer (NSCLC), PTEN deficiency is seen in up to 70% of cases. Moreover, PNKP inhibition has been shown to act as a sensitizing agent for topoisomerase I inhibitors, such as irinotecan. PNKP is a ubiquitous enzyme, thus its targeted inhibition in cancer over normal cells is of immense importance.

OBJECTIVES

The aim of the present study was to develop NSCLC targeted nanoparticles encapsulating a relatively potent novel PNKP inhibitor, namely A8384C63, and assess the anticancer activity of this formulation alone or in combination with irinotecan.

METHODS

- Micelles were composed of polyethylene oxide-poly(benzyl carboxylate-e-caprolactone)
- Maleimide groups on PEO segment were used for conjugation of H2009 1 peptide.
- Cy5.5-labelled nanoparticles were used to evaluate cell uptake using flow cytometry.
- Cytotoxicity of A8384C63 in NSCLC cell lines expressing different levels of PTEN expression with and without irinotecan treatment was assessed by MTS and colony-forming assays.

RESULTS

Table 1. Characterization of polymeric micelles.

<table>
<thead>
<tr>
<th>Polymeric micelles</th>
<th>Size (nm)</th>
<th>EE (%)</th>
<th>DL (%)</th>
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<tbody>
<tr>
<td>Plain-PEO-PBCL</td>
<td>51.4 ± 0.29</td>
<td>89.0</td>
<td>29.7</td>
</tr>
<tr>
<td>H2009-PEO-PBCL</td>
<td>68.5 ± 0.09</td>
<td>92.7</td>
<td>31.0</td>
</tr>
</tbody>
</table>

- Figure 2. (A) Analysis of different fractions after size exclusion chromatography (SEC). The yield of the coupling reaction between copolymer and peptide was determined by BCA assay. (B) Protein expression of αvβ6-integrins in two NSCLC cell lines, H1299 and H1975 cells.

- Figure 3. Effect of irinotecan treatment on metabolic activity (A and C) and on cell survival (B and D) in NSCLC cells with or without A8384C63 sensitization. Results of H1299 cells are shown in the left panel (A and B); and H1975 in the right panel (C and D).

CONCLUSION

The synthetic lethal relationship between PTEN expression and A8384C63 treatment in NSCLC cell lines was confirmed. Chemosensitizing activity of A8384C63 towards irinotecan in NSCLC cell lines was also effective. Finally, our data showed an enhancement in cell uptake of H2009-micelles in H1975 cells, which suggests a great potential for targeted delivery of A8384C63.

Taken together, this study implies a potential for polymeric micellar formulations of A8384C63 as mono-therapeutics in NSCLC cells with low PTEN expression and/or as targeted sensitizers to topoisomerase I inhibitors against NSCLC tumors.

REFERENCES


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