ABSTRACT SUMMARY

In order to construct a novel boron delivery agent for Boron Neutron Capture Therapy (BNCT) toward melanoma, we evaluated Kojic acid-appended carborane (CKA). Metastatic melanoma remains so highly lethal cancer. So, BNCT has been attracted great deal of attention as a potentially useful modality for this disease. Then, it has been said that kojic acid possesses an ability to whiten melanocytes by a strong tyrosinase inhibition. [1] This fact suggests that kojic acid possess a specific affinity for melanocytes. So, kojic acid is expected as effective ligand toward melanoma. For its hydrophobicity, we used various cyclodextrins as a solubilizer. Then, Inclusion complex prepared with hydroxypropyl-β-cyclodextrin (HP-β-CD) provides the highest concentration.

Cytotoxicity of the complex was estimated by WST-assay. Then, Uptake efficiency and cellular distribution of the complex was evaluated within the concentration estimated as low toxicity toward cells.

The therapeutic and antitumor efficacy of BNCT for murine with CKA/HP-β-CD was evaluated within murine survival. In conclusion, CKA/HP-β-CD is promising toward melanoma because of significant tumor-suppression effect toward tumor-bearing mouse.

INTRODUCTION

Boron Neutron Capture Therapy (BNCT) is a cell-selective radiation therapy for cancer. This therapy is performed by the alpha particles and lithium nuclei from boron neutron capture reaction. These particles causes cell destruction, bouncing out to maximum distance of 10 μm. This length of bouncing corresponds to the size of a cell. The success of BNCT depends on the delivery that $^{10}$B compounds accumulate effectively and deeply inside the tumor cells. Clinically, Boronophenylalanine (BPA) and Sodium boronocaptate (BSH) are currently available for BNCT as boron delivery agents but these boron delivery agents have some improvements: accumulation or selectivity for tumor tissue. [2] THE purpose of this paper, therefore, to construct a novel and effective boron delivery agent toward melanoma with Kojic Acid for BNCT.

EXPERIMENTAL METHODS

The cell melanoma line B16BL6 and colorectal cancer line colon26 were used. CKA was synthesized and supplied by Mr Kirihata (Research Center for BNCT, Osaka Prefecture University). Water-soluble CKA complexes were effectively prepared with HP-β-CD by using mixing with vortex-mixer. Boron concentration was estimated by ICP-AES. Cytotoxicity of the complex was estimated by WST-assay. Then, Uptake efficiency and cellular distribution of the complex was evaluated within the concentration estimated as low toxicity toward cells. The therapeutic and antitumor efficacy of BNCT for murine with CKA/HP-β-CD was evaluated within murine survival.

Figure 1: compound of CKA
RESULTS AND DISCUSSION

After addition of CKA/HP-β-CD to culture medium of B16BL6 and colon26, relative cell viability was estimated 24 hours. Then CKA/HP-β-CD didn’t show toxicity under 40 ppmB. Therefore, Uptake efficiency and cellular distribution of CKA/HP-β-CD was evaluated within 10 ppmB. CKA/HP-β-CD was taken up more efficiency B16BL6 than colon26. This fact indicates CKA/HP-β-CD possesses melanoma selectivity. Moreover, CKA/HP-β-CD was localized around nuclear in 1 hour after treatment. Therefore, CKA/HP-β-CD might perform BNCT effectively for its accumulation around nuclear.

For melanoma selectivity and accumulation around nuclear were confirmed in vitro, we evaluated the therapeutic and antitumor efficacy of BNCT for murine with CKA/HP-β-CD was evaluated within murine survival. CKA/HP-β-CD and L-BPA fructose complex were injected by i.p before irradiation toward tumor-bearing mouse. Neutron irradiation was performed at Kyoto University Research Reactor (5 MW, 18mins, 5.0×10^{12} neutron/cm^2). After irradiation, proliferation and antitumor efficacy of BNCT were improved within concentration-dependent and irradiation time-dependent. Moreover, CKA/HP-β-CD was found to be about as effective as L-BPA used as positive control.

CONCLUSION

In conclusion, CKA/HP-β-CD can deliver toward melanoma selectively and effectively. Therefore, CKA/HP-β-CD can improve the proliferation of the tumor-bearing mouse as effective as L-BPA. This delivery system is promising toward melanoma for BNCT.

REFERENCES


ACKNOWLEDGMENTS

We would like to gratefully thank Mr. Shinichiro Masunaga (Research Reactor Institute, Kyoto University) for their experimental support, especially in vivo.