CONCLUSIONS

Amanitin-based antibody-drug conjugates targeting the prostate-specific membrane antigen PSMA

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INTRODUCTION

Antitumoral activity of monomeric antibodies can be dramatically enhanced by conjugation to toxic small molecules. Despite the reported use of Kadcyla (T-DM1) and ado-trastuzumab emtansine (T-DM1) more than 10 years ago, only a few monoclonal antibodies (mAbs) have been translated into clinical practice. Recently, improved understanding of the targets and pharmacology of mAbs, targeting the human prostate cancer cell lines CWR-22Rv1, MDAMB-231, and PCa2b and PC-3 were obtained from the ATCC and grown according to the suppliers in a humidified incubator containing 5% CO2 and 95% air. Amanitin was covalently conjugated to lysine side chains of the antibody by stable and cleavable linkers to form amanitin-based antibody-drug conjugates (ADCs) (c). SEC-HPLC demonstrated low abundance of cross-linked protein & aggregates (c).

METHODS

Cell lines and antibodies. The human prostate cancer cell lines CWR-22Rv1, MDA-MB-231, PCa2b, and PC-3 were obtained from the ATCC and grown according to the suppliers in a humidified incubator containing 5% CO2 and 95% air. Amanitin was covalently conjugated to lysine side chains of the antibody by stable and cleavable linkers to form amanitin-based antibody-drug conjugates (ADCs) (c).

RESULTS

Structure of toxin-linker compounds

Effective toxin release by Cathepsin B using cleavable linker

Low abundance of cross-linked protein & aggregates

Antitumoral activity of single dose application

Cytoxicity on prostate cancer cells in vitro

Figure 4: BrdU-assay with PC cells and amanitin-based anti-PSMA ADCs.

Figure 6: CWR-22rv1 subcutaneous xenograft model. Amanitin ADCs were applied as single dose i.v. at 150µg/kg with respect to toxin.

Figure 5: (a) Growth arrest of LNCaP cells by addition of 100ng/mL IL-6.

Figure 7: (a) In vivo (b) In vitro antitumoral activity of amanitin-based anti-PSMA ADCs.

REFERENCES

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