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Abstract

In Vitro Characterization of an Anti-HER2 Affibody-Monomethyl Auristatin E Conjugate in HER2-Positive Breast Cancer Cells †

Isabella Damiani, Silvia Castiglioni, Valentina Rusconi, Clara Rossi, Alberto Corsini and Stefano Bellosta *

Department of Pharmacological and Biomolecular Sciences, University of Milan, 20133 Milan, Italy; isabella.damiani@unimi.it (I.D.); silvia.castiglioni@unimi.it (S.C.); valentina.rusconi@studenti.unimi.it (V.R.); clara.rossi3@studenti.unimi.it (C.R.); alberto.corsini@unimi.it (A.C.)

* Correspondence: stefano.bellosta@unimi.it

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Abstract: Antibody-drug conjugates (ADCs) are used in anticancer therapy with some limitations due to their molecular properties. An alternative to monoclonal antibodies is the affibody, composed of 58 amino acids, with lower binding affinities, small size, and rapid blood clearance and tissue distribution. We investigate the in vitro efficacy of a novel anti-HER2 ZHER2:2891 affibody conjugated to a cytotoxic drug auristatin E (MMAE) in HER2-positive human cancer cells. An adenocarcinoma cell line SK-BR-3, expressing high levels of HER2, and mammary gland adenocarcinoma MDA-MB-231, expressing basal levels of HER2, were treated with ZHER2:2891DCS-MMAE and trastuzumab (as a reference compound). ZHER2:2891DCS-MMAE induced a significant time-dependent toxic effect in SK-BR-3 cells. A 30% reduction in cell viability was found after 10 min exposure at 7 nM with an IC50 of 80.2 nM. On the contrary, MDA-MB-231 cells were not affected by the affibody complex. The HER2-specific cytotoxic effect of the ZHER2:2891DCS-MMAE has also been confirmed by measuring apoptosis by flow cytometry. In SK-BR-3 cells, the increasing concentrations of the conjugated affibody induced cell death after 10 min of treatment with the strongest effect observed after 48 h. Moreover, treatment with ZHER2:2891DCS-MMAE reduced (up to 50%) HER2 expression at both mRNA and protein levels in SK-BR-3 cells after 24 h of treatment. In conclusion, the cytotoxic conjugate based on the anti-HER2 affibody and MMAE efficiently interacts with HER2 over-expressing cancer cells, allowing the selective and specific delivery of the cytotoxic payload. The basal HER2 expressing cells are not the most affected probably due to a lower uptake of the drug conjugate. This confirms that affibodies may be used to target HER2 overexpressing cells while sparing normal cells.

Keywords: affibody; HER2; trastuzumab; breast cancer

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