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抗体偶联药物抗HER2单抗-MCC-DM1细胞毒活性检测方法的建立及其检测效果评价　　点此下载全文

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摘要：

　　目的：建立抗体偶联药物（antibody-drug-conjugate, ADC)抗人类表皮生长因子受体2（human epidermal growth factor receptor-2，HER2）人源化单抗-MCC-DM1的细胞毒活性检测方法，并评价该抗体偶联前后药物细胞毒活性的变化。方法：供试品为抗HER2-MCC-DM1原液及成品各3批，以抗HER2人源化单抗和抗HER2单抗-MCC-DM1标准品为参考品，利用CCK-8法、双荧光染色实验分别检测供试品和参考品对人乳腺癌BT-474细胞增殖的抑制作用，计算供试品相对百分数价，并比较抗体偶联前后该药细胞毒活性的改变；光学显微镜和荧光显微镜观察抗体偶联前后对BT-474细胞生存的影响。结果：抗HER2-MCC-DM1供试品及参考品在肿瘤细胞增殖抑制实验中均存在量效关系。3批原液和3批成品各经3次测定，对B7-474细胞增殖抑制活性的相对百分数价平均值在(92.50±8.80)% ~ (115.14±6.09)%，变异系数均小于15%。与抗HER2单抗原液相比，对应批次的抗HER2-MCC-DM1原液和成品各经3次测定，细胞增殖抑制活性平均值分别为偶联修饰前抗活性的（326.72±21.58）%和（315.76±34.90）%。与偶联前抗体组相比，抗体偶联药物组细胞圆缩和死亡明显增多。结论：所建立的体外细胞增殖抑制法可用于抗体偶联药物抗HER2-MCC-DM1的细胞毒活性检测，其重复性好、准确性高，可应用于ADC药物的质量控制及有效性评价。

关键词：单克隆抗体　抗体偶联药物　抗HER2-MCC-DM1　细胞毒活性　质量控制

**Development and evaluation of detective methodology for cytotoxic activity of an anti-human epidermal growth factor receptor-2-MCC-DM1 against breast cancer cells**　Download Fulltext

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**Abstract:**

　　Objective: To develop and evaluate the methodology for biological assessment of anti-HER2-MCC-DM1, an antibody-drug-conjugate (ADC) consisting of an anti-human epidermal growth factor receptor 2 (HER2) monoclonal antibody conjugated to the maytansinoid emtansine (DM1) via nonreducible thioether linkage (MCC) in breast cancer cells. Methods: Representative samples were collected from three batches of bulk drug and three batches of final products, along with the manufacturer's validated reference standard. Breast cancer BT-474 cells were treated with the test samples and reference standard respectively. Five days after treatment, cell proliferation inhibition and cell viability were determined by colorimetric assay using a commercial cell counting kit and dual fluorescent staining analysis. Experiments were repeated three times. Results: Both test samples and reference standard of anti-HER2-MCC-DM1 inhibited BT-474 cell proliferation in a dose-dependent manner. The variation coefficient of percent inhibition within the three experiments was less than 15% for both test samples and reference standard. Compared with the nude anti-HER2 antibody, the bulk drug and final product increased BT-474 cell proliferation inhibition by （326.72±21.58）% and （315.76±34.90）% respectively. HER2-MCC-DM1 effectively induced BT-474 cell shrinkage and death as revealed by both light microscopy and fluorescence microscopy. Conclusion: The biological assessment of anti-HER2-MCC-DM1 in breast cancer BT-474 cells　in vitro　, developed in this study, is highly reproducible and accurate, thus offering a promising method for quality control and evaluation of ADCs.

Keywords:monoclonal antibody　antibody-drug-conjugate　anti-HER2-MCC-DM1　cytotoxic activity　quality control

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