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论著

4-［4″-(2″, 2″, 6″, 6″-四甲基-1″-哌啶氮氧自由基)氨基］-4′-去甲表鬼臼毒素对K562/ADM细胞的抑制作用

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摘要 目的 比较4-［4″-(2″, 2″, 6″, 6″-四甲基-1″-哌啶氮氧自由基)氨基］-4′-去甲表鬼臼毒素（GP-7）对多药耐药人慢性粒细胞白血病K562的多柔比星耐药株细胞（K562/ADM细胞）的抑制作用是否优于依托泊苷。方法 以依托泊苷和K562细胞为对照，用不同浓度GP-7处理K562/ADM细胞不同时间，MTT比色法测定细胞增殖，流式细胞仪测定细胞周期和细胞凋亡率，普通光学显微镜观察细胞凋亡形态，琼脂糖凝胶电泳观察细胞DNA凋亡性降解。结果 8～128 mol·L^{-1} GP-7处理48 h或64 μmol·L^{-1} GP-7处理24～72 h，GP-7对K562/ADM细胞的增殖抑制呈剂量依赖性（r=0.947，P<0.05)和时间依赖性(r=0.999，P<0.01)。GP-7及依托泊苷对K562/ADM的IC_{50}分别为(45.9±1.8)及(68.7±4.6)μmol·L^{-1}；64 μmol·L^{-1} GP-7作用48 h可使G_2/M期细胞明显增多，相同情况下依托泊苷则使S期细胞明显增多；GP-7可引起K562/ADM和K562细胞凋亡，但其引起的K562/ADM和K562细胞凋亡率与依托泊苷无明显差异；GP-7可引起K562/ADM和K562细胞典型的凋亡形态学变化和DNA凋亡性降解，但GP-7引起的K562/ADM细胞DNA凋亡性降解弱于K562细胞；128及256 μmol·L^{-1} GP-7或依托泊苷处理K562/ADM和K562细胞48 h，GP-7诱导DNA凋亡性降解的作用强于依托泊苷，但32和64 μmol·L^{-1}时作用则相反。结论GP-7可抑制多药耐药白血病细胞株K562/ADM的增殖,诱导细胞凋亡。GP-7抑制多药耐药白血病细胞株K562/ADM的作用优于依托泊苷。

关键词 鬼臼毒素 白血病 髓样 慢性 细胞凋亡 抗药性 多药

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Inhibitory effect of 4-［4″-(2″, 2″, 6″, 6″-tetramethyl-1″-piperidinyloxy) amino］-4′-demethylepipodophyllotoxin on K562/ADM cells

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Abstract

AIM To compare whether the antitumor effects of 4-［4″-(2″, 2″, 6″, 6″-tetramethyl-1″-piperidinyloxy)amino］-4′-demethylepipodophyllotoxin (GP-7)on multidrug-resistant human chronic myelogenous leukemia K562/ADM cells (K562 cells resistant to doxorubicin) are superior to etoposide. METHODS With etoposide and K562 cells as controls, K562/ADM cell was treated with GP-7, its cell proliferation was detected by MTT assay, cell cycle and apoptosis ratio were detected by flow cytometry, apoptotic morphology was observed by light microscopy, and apoptotic DNA fragmentation was detected by agarose gel electrophoresis. RESULTS When treated with 8-128 μmol·L^{-1} GP-7 for 48 h or 64 μmol·L^{-1} GP-7 for 24－72 h, the proliferation of K562/ADM cells was inhibited in a concentration or time dependent manner（r=0.947，P<0.05; r=0.999，P<0.01, respectively). The IC_{50} of GP-7 and etoposide to K562/ADM were (45.9±1.8) and (68.7±4.6)μmol·L^{-1}, respectively. When treated with GP-7 of 64 μmol·L^{-1} for 48 h, K562/ADM cells were arrested at G_2/M phase, whereas etoposide caused S phase aggregation of the cells. GP-7 could induce apoptosis of both K562/ADM and K562 cell lines, there was no significant difference between GP-7 and etoposide-induced apoptotic ratio. GP-7 could also induce typical apoptotic morphology changes and DNA fragmentation of K562/ADM and K562 cells, but DNA fragmentation induced by GP-7 in K562/ADM cells was weaker than that in K562 cells. When treated with GP-7 or etoposide for 48 h, 128 or 256 μmol·L^{-1} of GP-7 induced more DNA fragmentation than that of etoposide did, but 32－256 μmol·L^{-1} GP-7 induced less DNA fragmentation than that of etoposide did. CONCLUSION GP-7 may inhibit multidrug-resistant leukemia K562/ADM cells proliferation and induce apoptosis. Its inhibitory effect on K562/ADM cells is superior to etoposide.

Key words podophyllotoxin leukemia myeloid chronic apoptosis drug resistance multiple

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