THE EFFECT OF ACLARUBICIN ON CELL CYCLE DISTRIBUTION OF NORMAL AND TRISOMIC HUMAN FIBROBLASTS

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Aclarubicin (ACL) possesses many properties that distinguish it from other anthracycline antibiotics. It differs from daunorubicin and doxorubicin both in the structure of aglycone and in possessing trisaccharide moiety, consisting of rhodosamine, 2-deoxyfucose and cinerulose A. Compared to the other anticancer antibiotics, there is little information in respect to the mechanism of ACL activity in trisomic cells derived from patients with Down syndrome (DS). Therefore this study aimed at investigating the ACL effect on cell cycle of normal (S-2 cell line) and trisomic (BB cell line) fibroblasts.

Flow cytometry analysis of cell cycle of trisomic BB cells showed that its distribution mirrored slow proliferation rate of this cell line. Most cells (over 70% during the first three days after plating and above 80% after longer time period) were present in the G1 peak representing non-dividing cells. Proliferating cells (S phase of the cell cycle) constituted the smallest population (bellow 7%) and decreased progressively to as low as to about 3% at the end of the investigated post-treatment period (144 h). ACL did not alter significantly the cell cycle distribution of BB cells. Except for small (about 12%) increase in the G1 cell number at expense of both S and G2/M cell populations, which number decreased by more than a half after 72 h of the post treatment. Similar pattern of changes in the proportion of untreated and drug-treated cells being in the particular phase of the cell cycle confirmed the fact that short treatment (2 h) with the IC_{50} concentration of ACL is insufficient to affect significantly the ability of these cells to proliferate.

Different pattern of cell cycle was observed in normal S-2 cells. The amount of non-dividing G1cells represented about half of the entire cell population. Ac-DEVD-CHO inhibitor did not show any significant influence on the proportion of cells between the particular cycle phases. In contrast to trisomic BB cells a progressive arrest of S-2 cells in the G2/M phase was observed after longer (above 72 h) post-incubation period in cells treated with ACL. The most notable accumulation of cells in the G2/M phase took place during the 72–96 time interval. After then the number of the G2/M arrested cells did not change significantly. G2/M arrest was not observed in cells pretreated with the caspase-3 inhibitor Ac-DEVD-CHO and exposed to ACL in the presence of the inhibitor. This might suggest that cell cycle arrest in the G2/M phase is an important factor for the apoptotic cell death of S2 cells. Comparison of the percentage of BB and S2 cells in the apoptotic sub-G1 peak showed that faster proliferating S2 cells were less prone to induction of apoptosis by ACL than slowly proliferating BB cell line. This might suggest that S2 cells probably repaired more efficiently DNA damages caused by ACL. While number of apoptotic cells in both cell lines was negligible and rather comparable during the first 48 h after their incubation with ACL (7–8%) it raised considerably faster in BB cells than in S2 cells in the longer post-incubation period (72–144 h).