ACTIVITY *IN VITRO* AND *IN VIVO* OF NEW DERIVATIVES OF ANTHRACYCLINE ANTIBIOTICS

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Anthracycline antibiotics belong to a broad spectrum of antitumor drugs which for a period of almost three decades have been extensively applied for the treatment of patients with different tumor deseases, particularly with acute leukemia or solid tumors. The basic clinical problems connected with using of these antibiotics in therapy appeared to be their toxicity, mainly cardiotoxicity and the drug resistance of tumor cells to these drugs.

In the search for new analogs of anthracycline antibiotics with lower toxicity or/and higher cytotoxic activity, a series of new derivatives with modified amino group in daunosamine moiety have been synthesized. These derivatives revealed similar or higher antiproliferative activity than the parent drugs. Toxicity of these analogs were significantly lower, as shown by the values of LD_{50} being from 2 to 20 fold higher in comparison to the parent antibiotics. The results of determinations of cardiotoxicity, using male mice indicated that cardiotoxicity of the new analogs is also significantly lower than that of the referential antibiotics. Besides, the majority of the new analogs apppeared to be able to overcome, completely or partially, drug resistance of cancer cells.

On the base of these results the analogs of daunorubicin, doxorubicin, epidaunorubicin and epidoxorubicin, containing morpholine ring at the 3' position, were selected to a preliminary *in vivo* screening. The transplantable mouse tumor models such as P388 leukemia, L1210 leukemia, colon carcinoma C38 and breast carcinoma 16/C growing in (BALB/c x DBA/2)F1 or C57B1/6 x DBA/2(BDF1) mice were applied as the models in these studies. The new derivatives and referential antibiotics were administered intraperitoneally. The obtained results have shown that cytotoxic activity *in vivo* of the new analogs of daunorubicin and epidaunorubicin against P388 leukemia were higher then that of the parent drugs *e.g.* the value of ILS (increase in life span) for these derivatives were 49.6% and 33.6% and for the referential antibiotics 36% and 28% respectively. The activity of the new analogs against rectal carcinoma C38 and breast carcinoma 16/C were lower than that of the referential drugs.

It should be pointed out that the new derivatives of anthracycline antibiotics only in some cases revealed the increase of activity *in vivo* but because of lower toxicity and possibility to overcome the drug resistance to cancer cells may appear as valuable drugs in antitumor therapy.