LOW HEART AND SKIN TOXICITY OF A TETRAHYDROPYRANYL DERIVATIVE OF ADRIAMYCIN (THP-ADM) AS OBSERVED BY ELECTRON AND LIGHT MICROSCOPY

Sir:

Cardiotoxicity and alopecia caused by anthracyclines were examined in an experimental model in which golden hamsters were treated three times a week with i.p. doses equivalent to 3/4 of the optimally oncostatic dosages against murine L1210 leukemia, where they were given at days 1, 5 and 9 after tumor cell inoculation. Each drug was administered to 21 hamsters, and every week 3 animals from each group and 3 control animals were sacrificed. Relevant tissues were quickly removed and immediately processed for examination.

In preceding publications[1,2] it was shown, by electron microscopy (EM), that AD32 is less myocardiotoxic than adriamycin (ADM), detorubicin (DTR), daunorubicin (DNR), 4′-*epi*-adriamycin (eADM), adriamycin hydrochloride (ADMh) and rubidazon (RBZ); and that aclacinomycin (ACM) is less cardiotoxic than AD32. By light microscopic (LM) studies of skin, it was also observed that ACM and AD32 preserved the normal histological structures of skin, without causing alopecia, as contrasted with the 6 other anthracyclines which caused marked atrophy of all epidermic layers and loss of hair (alopecia)[1,2].

The most recent anthracycline studied by these techniques is THP-ADM, a new Japanese drug[3], at a dosage of 4 mg/kg i.p. This communication, briefly reports our findings concerning the EM alterations of the myocardium, the LM lesions of the skin and the mortality of this drug as compared with those of the 8 preceding anthracyclines studied.

Mortality was very high for the animals receiving the first 6 drugs (ADM, DTR, DNR, eADM, ADMh and RBZ), and all animals died before the end of the 4th week of treatment. By contrast, the mortality was very low for animals receiving the other three drugs (ACM, AD32, and THP-ADM). Only one out of 21 ACM and AD32 treated hamsters died during the 4 weeks of treatment, and there were no deaths in the group of THP-ADM treated animals at the end of the 4th week of treatment. As with ACM and AD32 treated animals, all THP-ADM treated hamsters preserved their good general status, without loss of weight and without digestive trouble. All animals treated with the other six anthracyclines (ADM, *etc.*) showed 30% to 40% weight losses and severe digestive troubles with severe diarrhoea.

At the end of the first and second weeks of treatment, EM examination of the myocardium of both the THP-ADM and the ACM treated hamsters showed very rare and mild lesions. Some myocytes had swelling of the mitochondriae, clearing of their matrices, and lysis of the crests. Generally, mitochondriae, myofilaments and intercalated discs were as well preserved as those in the controls. The myocardium of all animals treated with ADM, DTR, DNR, eADM, ADMh and RBZ showed very severe alterations by EM, *viz.*, swelling of mitochondriae with lysis of their crests, dilation of sarcoplasmic reticulum, separation and lysis of myofilaments with disruption of z-band registry, separation of fascia adherens of intercalated discs, vacuolization of the cytoplasma and formation of myelinic figures. At the end of the first and second weeks of AD32 treatment, lesions in these animals were less marked than those seen in the animals treated with the preceding 6 antibiotics but changes were apparent in the mitochondriae, the myofilaments and intercalated discs.

At the end of the 4th week of treatment, all surviving THP-ADM treated hamsters had very mild and rare EM alterations of their myocardium, with moderate lesions of the mitochondriae, myofilaments and intercalated discs.

Two months after THP-ADM treatment had been terminated, an EM study of the myocardium of sacrificed animals revealed that there was recovery in the myocardial alterations, as was also observed with ACM and AD32 treated hamsters[1,2]. The myofibrils and mitochondriae were generally as well preserved as those in the controls.

LM studies of the skins of the THP-ADM treated animals showed normal histologic structures of the epidermic layers and hair (without alopecia) as in ACM and AD32 treated animals, even after 4 weeks of treatment. Histopathologic studies of the skins of the animals treated with the six other groups of antibiotics (ADM, *etc.*) showed degenerative lesions with very marked atrophy of epidermic layers and loss of hair (alopecia).

These studies indicate that after i.p. administration of THP-ADM to golden hamsters comparative studies of the mortalities, EM alterations of the myocardia and the histopathologic lesions of skins show that, under our experimental conditions, THP-ADM is the least toxic and particularly the least cardiotoxic anthracycline. ACM and AD32 are somewhat more toxic.

If these lower toxicities and good antitumor activities are reconfirmed by clinical observations with these three drugs, these will offer important contributions to the chemotherapy of neoplasias.

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