THERAPEUTICAL EFFECT OF 4'-DEOXY-4'-IODODOXORUBICIN-LOADED LAK CELLS IN MICE BEARING LUNG METASTASES

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INTRODUCTION

Many attempts have been made to deliver antineoplastic drugs to the tumor site in order to increase therapeutic activity and reduce systemic toxicity. We previously observed that adoptive transfer of tumor-specific cytotoxic T lymphocytes (CTL) and lymphokine-activated killer (LAK) cells loaded with ricin into tumor-bearing mice induced a temporary inhibition of local or metastatic tumor cell growth (1,2); however, the high toxicity of ricin constitutes a major limit to this immunotherapeutical approach. In this study we further investigated the therapeutic activity of LAK cells loaded with two anthracyclines, Adriamycin (ADR) and 4'-Deoxy-4'-iododoxorubicin (IDX), following adoptive transfer into mice bearing pulmonary metastases.

RESULTS AND DISCUSSION

LAK cells were incubated with 10 μM ADR for 2 hours, or 10 μM IDX for 45 min. After extraction with EtOH-HCl and subsequent spettrofluorimetric evaluation, ADR and IDX incorporation was estimated as 380 and 570 ng/10^6 cells, respectively. LAK cells released approximately 40-50% of the total internalized drug during the first 10 min., thereafter a lower release was observed. Drug treatment did not reduce LAK cell cytotoxic activity at the end of incubation time, but a gradual loss of activity was observed in the following 6 hours.

Previous studies demonstrated that i.v. injected LAK cells preferentially localize in the lungs of recipient mice as early as 1 hour after inoculation (3,4). Therefore, the therapeutic effect of adoptive transfer of ADR- and IDX-treated LAK cells was evaluated in C57BL/6 mice bearing lung metastases induced by the melanoma cell line B16F1. Two days after tumor cell inoculation, mice received i.v. $50x10^6$ drug-treated LAK cells; the animals were sacrificed 20 days later and lung metastases counted. As shown in tab. 1, ADR-treated LAK cells did not affect the growth of lung metastases compared to controls, while IDX-treated LAK cells brought about a strong reduction of metastases. No therapeutic effect was observed in control mice injected with the same number of untreated LAK cells or with doses of free anthracyclines that, on the basis of spettrofluorimetric analysis, corrisponded to the amount carried by the transferred LAK cells. The different protection observed between ADR- and IDX-treated LAK cells may in part be explained by the characteristics of the drugs; IDX is more lipophilic than ADR (5), so that higher intracellular concentrations can be achieved not only in LAK cells, which deliver the drug, but also in surronding tumor cells when the drug is released.

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TAB. 1

ANTI-TUMOR EFFECT OF ANTHRACYCLINE-TREATED LAK CELL ADOPTIVE TRANSFER

Number of lung metastases after indicated treatment

	NONE+	LAK CELLS*	ADR-LOADED LAK CELLS	IDX-LOADED LAK CELLS	FREE ADR@	FREE IDX@
EXPT. 1	91±21	92±12	82±36	ND	88±22	ND
EXPT. 2	25± 8	23± 6	ND	2±1	ND	17±5

* C57BL/6 recipient mice were i.v. injected with $50x10^6$ LAK cells, obtained by culturing syngenic spleen cells for 7 days with rIL-2 200 U/ml

\+ mice received $2x10^5$ and 10^5 B16F1 tumor cells in expt. 1 and 2 respectively

@ mice received 20 μg of ADR in expt. 1 and 30 μg of IDX in expt. 2

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