Time course of Paclitaxel-induced apoptosis in an experimental model of virus-induced breast cancer.

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Abstract

Early assessment of the efficacy of treatment is important in patients with breast cancer, whose routine adjuvant regimen frequently includes chemotherapy. Irrespective of the exact mechanisms involved in induction, the common early phenotypic marker of apoptosis is the expression on the outer cell membrane surface of phosphatidylserine, which avidly binds annexin V. (99m)Tc-labeled annexin V has been proposed for in vivo scintigraphic detection of apoptosis, albeit with contradicting results. This study was performed to define the time course of apoptosis induced by the chemotherapeutic agent paclitaxel in a model of virus-induced murine breast cancer.

METHODS: The RIII virus induces an estrogen-dependent, slow-growing breast cancer; BALB-c/cRIII female mice with breast tumors averaging 10 mm were studied, both in baseline conditions and at various times after the intravenous administration of paclitaxel (equivalent to a human dose of 20 mg/70 kg of body weight). The biodistribution of (99m)Tc-annexin V was evaluated at baseline and then at 1, 3, 6, and 24 h after paclitaxel administration. Apoptotic and antiapoptotic markers were also evaluated in tumor samples obtained at the same time points: DNA breaks (terminal deoxynucleotidyl transferase biotin-dUTP nick-end labeling [TUNEL]), active caspase-3, apoptosis-inducing factor, and Bcl-2 protein.

RESULTS: Baseline uptake of (99m)Tc-annexin V in breast tumors was about 2-fold higher than the uptake in normal breast tissue (demonstrating some ongoing apoptosis); tracer uptake increased at 1 and 3 h after paclitaxel administration (to almost double the baseline value) and then declined to levels even lower than baseline. Although no activation of the apoptosis-inducing factor mechanism was detected, a peak in TUNEL-positive tumor cells was reached 3 h after paclitaxel administration (to more than 6-fold the baseline level). The antiapoptotic marker Bcl-2 exhibited a biphasic pattern, with a maximum drop at 3 h, followed by return toward baseline levels at 6 h.

CONCLUSION: These results define the time course of various biologic events taking place in this model of murine breast cancer after a proapoptotic insult (single-dose paclitaxel). Although confirming that in vivo uptake of (99m)Tc-annexin V reflects the degree of apoptosis, the study also suggests that the apoptotic response to antitumor therapy may differ from tumor type to tumor type. Therefore, contradicting results previously reported may depend on an inadequate time window chosen for imaging with (99m)Tc-annexin V.