Sensitivity to Antineoplastic Agents of Human Tumor Strains in Immunodeficient Mice

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A total of 19 human tumor strains transplanted to athymic mice and rats are tested for their sensitivity to antineoplastic agents of different classes including alkylating compounds, platinum complexes, and nitroso compounds. It is noted that the observed growth patterns of these strains and their recorded differential sensitivities to the compounds tested can help in selecting appropriate models for preclinical trials of new compounds and for biomedical experiments.

Key Words: *human tumor strains; athymic mice and rats; antineoplastic agents*

At the Cancer Research Center, Moscow, a collection of human tumor strains for transplantation to athymic mice and rats has been set up through serial transplantations of surgical specimens or cultures of human tumors. Because of their stability and their morphological identity to the original tumors, these strains can yield experimental results that are highly consistent and comparable to those obtained clinically [1].

In the work reported here, 19 of these strains were tested for their sensitivity to novel potential antineoplastic drugs of different chemical classes undergoing the final phase of their preclinical trials. The growth pattern of each strain was characterized and its responses to preparations of particular classes were evaluated with a view to predicting their future clinical efficacy.

MATERIALS AND METHODS

Cells of human tumor strains suspended in Hanks' balanced salt solution were transferred subcutaneously to BALB/c-derived athymic mice aged 6-8 weeks and to randomly bred athymic rats aged 4-6 weeks.

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The growth kinetics of each strain was monitored by measuring tumor sizes, the periods of maximal tumor growth, and the survival of untreated (control) animals and of those treated with potential antineoplastic drugs of different classes (alkylating compounds, nitroso compounds, and platinum complexes) using optimal doses and times and routes of administration. The control and test groups each comprised 4-6 animals, and drug treatment was started 7 to 15 days after tumor cell transplantation, when the tumors were 0.3-1.5 cm^3 in volume. The antineoplastic potency of each compound was estimated by the percentage inhibition of tumor growth as calculated from differences in tumor volumes and survival times between control and treated animals. The results were processed statistically.

RESULTS

A total of 19 tumor strains belonging to 13 nosological entities were studied, including Burkitt's lymphoma (n=1), colonic adenocarcinoma (n=3), pulmonary carcinoma (n=2), stomach cancer (n=1), hepatocellular carcinoma (n=1), bladder cancer (n=1), renal cancer (n=2), melanoma (n=3), chorioepithelioma (n=1), uterine cancer (n=1), fibrosarcoma (n=1), Ewing's sarcoma (n=1), and rhabdomyosarcoma (n=1).

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The strains each showed a distinctive growth kinetics. Mice developed tumors ranging in volume from 7 to 25 cm^3 on average and survived for periods from 19 to 80 days. Rats developed tumors 2 to 10 times larger and survived 1.5 times longer, on average, than did the mice grafted with the corresponding tumors.

The tumor most sensitive to chemotherapy proved to be the Burkitt's lymphoma. In both mice and rats, its growth was inhibited 90% to 100% by the six agents tested two complex alkylating compounds, two nitroso compounds, and two platinum complexes; in some cases, its complete regression was observed.

The responses of epithelial tumors depended on their strain and/or the drug used. Of three colonic adenocarcinomas (Nos. 1, 2, and 7), the most responsive one was № 7 (its growth was 70 to 80% inhibited by the hormonal cytostatic and the alkylating pyrimidine) and the least responsive was № 1. Strongly marked responses were exhibited by both lung cancer strains to the alkylating compound and to both nitroso compounds (growth inhibitions of 63 to 98% were noted). Both renal tumor strains were highly responsive to the hormonal cytostatic, platinum compounds, and nitroso compounds (their growth was inhibited 63-81%) and less sensitive to the sarcolysin peptide (47% inhibition). Moderately sensitive were the stomach cancer, hepatocellular carcinoma, and bladder cancer (transitional cell carcinoma) strains: the inhibition of their growth by the alkylating and nitroso compounds amounted to 50-80%.

Of the three melanomas strains (Nos. 1, 2, and 3), the most sensitive was № 1 (67-98% inhibition) and the least, № 3. The chorioepithelioma and (weakly differentiated) uterine carcinoma strains were sensitive to the hormonal cytostatic in both mice and rats, while the fibrosarcoma, Ewing's sarcoma, and rhabdomyosarcoma strains were sensitive to the hormonal cytostatic and nitroso compounds in rats (50-80% inhibition).

Antineoplastic activity was manifested by the drugs after one or two parenteral administrations and persisted for 10 to 20 days. As a rule, however, the treated animals did not survive significantly longer than the controls. Marked increases in the survival rate were observed for alkylating compound-treated animals with hepatocellular carcinoma (80%) and with bladder cancer (100%). The hormonal cytostatic increased 1.5-fold the survival of animals with renal cancer, uterine cancer, chorioepithelioma, or fibrosarcoma; the platinum complexes prolonged the survival of mice with melanoma № 1 and with Burkitt's lymphoma.

Thus, the tumor strains tested displayed well-differentiated sensitivities to the compounds of different classes used, and these differential sensitivities are comparable to the drug sensitivities (and drug resistances) shown by the corresponding tumors in clinical settings. Burkitt's lymphoma, for example, is a tumor that is also sensitive clinically, and it can therefore serve as an appropriate model in the screening of new compounds for antineoplastic activity. The findings that the melanoma strains and the renal cancer strain are sensitive to the platinum complexes used (oxoplatinum and cycloplatam) make it possible to recommend these complexes for clinical use, notably in polychemotherapy and in cases of recalcitrant renal cancer [2,3].

The identified individual growth patterns of particular tumor strains and their differential sensitivities to drugs of different classes can help in selecting strains appropriate to particular research objectives and in comparing alternative therapies.

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