A Methodological Approach to the Prediction of Anticancer Drug Effect in Humans

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ABSTRACT

Tumor cells from animals and humans were treated with drugs under tissue culture conditions. Tumor cells from the sensitive L1210 model were studied first. A dose-response curve was derived between drug exposure and subsequent cytotoxicity in L1210. The concentration of drug and duration of exposure were factors critical to the subsequent development of in vitro cytotoxicity. The in vitro dosage which effected 50% leukemic cell death in L1210 cells correlated with reported in vivo drug levels. Other tumor models and human neoplastic cells were studied at this dosage level. A good correlation was noted in these studies between the in vivo responsiveness and the in vitro chemotheraphy results in both animals and humans. It was suggested by these results that it may be possible to predict cancericidal drug activity for individual neoplasms by assaying the tumor cells in vitro for drug sensitivity.

INTRODUCTION

An extensive international cancer research effort over the last 30 years has developed effective chemotherapy (26). These agents, while effective in some patients, are totally ineffective in others. Presently, it is not possible to predict drug activity accurately for individual neoplasms. Several investigators have studied the relationship between the tissue culture and the host response to chemotherapy (3, 6, 7, 9, 13-16, 20, 22, 25, 28-30, 33, 34, 44, 48-51).

Most investigations were conducted before pharmacokinetic studies of the anticancer agents were completed. Additionally, earlier studies could not take into account the importance of cycle-specific and cycle-nonspecific drug properties. Despite these considerations, early investigators did report correlations between in vivo and in vitro drug treatment. With current concepts in mind, we undertook a series of studies in both animals and human tumor models. We derived a series of in vitro tests that correlated with in vivo response to chemotherapy in both animals and humans.

MATERIALS AND METHODS

Preclinical Studies

Animals. Six-week-old female BALB/c $\times$ DBA/2-J F1 (hereafter called CD2F1) and C3H/HeJ mice from The Jackson Laboratory, Bar Harbor, Maine, and 6-week-old female BALB/c mice from Laboratory Supply, Indianapolis, Ind., were acquired and used in these experiments. One sex was used for all experiments.

Tumors. L1210 leukemia was obtained from the Southern Research Institute, Birmingham, Ala., and was maintained by serial i.p. transplantation into CD2F1, mice. Murine Myeloma MOPC 104E was received from the National Cancer Institute, Bethesda, Md., and was serially maintained as an ascitic tumor in BALB/c mice. MOS was obtained from Case Western Reserve University, Cleveland, Ohio, and was transplanted serially in C3H mice by s.c. injection.

Tissue Culture Conditions. All in vitro experiments were carried out in Medium 199 containing 0.7 mM glutamine, Hanks' balanced salt solution, 25 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid buffer, 10% fetal calf serum, penicillin (50 units/ml), and streptomycin (50 $\mu$g/ml) at 37°C unless otherwise specified.

Drugs. Adriamycin (Adria Laboratories, Wilmington, Del.) and vinblastine (Lilly and Company, Indianapolis, Ind.) were procured commercially. BCNU and cis-platinum were obtained from the Division of Cancer Treatment, National Cancer Institute, Bethesda, Md.

Cytotoxicity Assay. Cytotoxicity was measured with the trypan blue dye exclusion test. Cells were incubated for 4 min with 0.167% trypan blue and 5% fetal calf serum. Viable cells were identified by their ability to exclude dye, whereas dye stained nonviable cells. At least 100 cells were counted for each experimental value recorded. The CI was computed by the following equation:

$$CI = 100 \times \left(1 - \frac{\% \text{ viable treated cells}}{\% \text{ viable control cells}} \right)$$

The values expressed represent the mean ± S.E. of at least 4 experiments.

Drug Concentration Studies. A single antineoplastic agent was suspended in tissue culture medium and diluted to a variety of drug concentrations. L1210 tumor cells were harvested and were added to the medium containing drug. After 24 hr of drug exposure, the CI was measured. Initial experiments involved log variations of drug concentration. A log range of drug concentrations associated with cytotoxicity (CI ≥ 20) was identified. This log range was then further investigated at intermediate values. Our lowest drug concentration associated with measurable cytotoxicity (CI ≥ 20) after 24 hr of drug exposure was identified for further study.

The abbreviations used are: MOS, murine osteosarcoma; BCNU, 1,3-bis(β-chloroethyl)-1-nitrosourea; cis-platinum, cis-dichlorodiammineplatinum(II); CI, cytotoxicity index.
Duration of Drug Studies. The duration of drug exposure required to effect cytotoxicity was studied. L1210 tumor cells were incubated for variable periods with the drug at the lowest cytotoxic (CI ≥ 20) concentration. The drug was then removed, and the tumor cells were incubated in a drug-free environment for 48 hr. The CI was then measured at 48 hr. A dose-response curve was defined involving 3 variables: (a) concentration of drug exposure; (b) duration of drug exposure; and (c) cytotoxicity due to drug exposure. All experiments critical to the definition of the dose-response curve were repeated in quintuplicate with controls on separate days.

In Vivo Correlation Studies. These studies involved tumor cells from MOPC 104E myeloma and MOS, as well as L1210 leukemia. Tumor cells were either aspirated from the peritoneum of ascites-bearing mice or harvested from solid tumors by sacrificing the tumor-bearing animal. Solid tumors (MOS) were minced and then repetitively treated with 0.1% pronase for 20 min at room temperature with gentle agitation. The cells were washed 3 times to remove the enzyme. A representative exposure time and concentration of the drug were chosen on the basis of previous studies. Tumor cells from these tumor models were exposed under derived conditions to the studied drug. After drug exposure, the tumor cells were incubated for 48 hr in a drug-free medium, and the CI was measured.

Clinical Studies

Patient Characteristics. Patients were studied if: (a) a pathological diagnosis of malignant lymphoma was established; (b) the malignant tissue was available for study; (c) measurable parameters of disease were present; and (d) the patient was a candidate for single-agent therapy with either BCNU or Adriamycin. Prior chemotherapy and radiotherapy were allowable provided that none of the agents under study had been previously administered to the patient. All prior antineoplastic treatment was terminated at least 30 days before study entry.

In Vitro Studies. After removal, a pathologically enlarged lymph node was surgically sectioned into 2 parts, with one-half being examined in the routine pathological fashion. The other half was teased aseptically in tissue culture medium. After the node was teased apart, the supernatant was washed, and we carefully layered it (employing the method of Böyum (8, 24, 38, 41)) on top of Isopaque-Ficoll in a test tube. This was then centrifuged at 400 × g for 40 min at room temperature. The interface lymphocytes were then carefully removed, washed twice, and suspended in tissue culture medium. The lymphocytes were exposed to antineoplastic agents in vitro by the previously described technique. Two days later the CI was measured. These experiments were conducted in quintuplicate with an estimate of mean ± S.E. It was not ethically possible to study tumor preparations repetitively on different days, since each study requires freshly biopsied human tumor tissue.

Treatment Program. BCNU was given in a dosage of 150 mg/sq m every 6 weeks. Adriamycin was given in a dosage of 60 mg/sq m every 3 weeks or 20 mg/sq m weekly, depending upon the preference of the patient and his physician. Concurrent steroid therapy was permitted if the patient had received corticosteroids for more than 2 months prior to the study.

RESULTS

Derivation of in Vitro Dose-Response Curve. The asynchronous L1210 cells were followed at 6, 12, and 24 hr for the development of cytotoxicity while being continuously exposed to cytotoxic drugs. Essentially no cytotoxicity could be detected before 24 hr. At 24 hr, the leukemic cells were shown to be sensitive to cancecidial drugs at a variety of concentrations. The sensitivity of L1210 to each of the drugs appeared to be dose dependent. At concentrations of 2 μg of Adriamycin per ml, 0.4 μg of vinblastine per ml, 20 μg of BCNU per ml, and 20 μg of cis-platinum per ml, each drug produced a CI greater than 20% when continuously incubated for 24 hr with L1210 leukemia (Chart 1).

Having determined a cytotoxic concentration, the duration of drug exposure was varied. Onset of cytotoxicity was noted to begin at 24 hr after drug exposure. The CI tended to increase from 24 to 36 hr after treatment. Variation of CI was not seen beyond 48 hr. Measurement of CI after variable times of drug exposure was conducted at 48 hr. Short drug exposures produced no cytotoxicity, while prolonged drug incubation regularly produced uniform cytotoxicity. The measurement of duration of drug exposure and subsequent cytotoxicity away from the extremes of either 0 or 100% cytotoxicity resulted in the relationships shown in Chart 2. A linear regression line was calculated from the derived experimental data through the least squares estimate. The coefficient of correlation (r²) of the derived equation was 0.97 for each of the 4 drugs tested.

Selection of In Vitro Dosage. The in vivo serum level of all 4 antineoplastic agents has been reported (1, 4, 5, 10-12, 31, 32, 35-37, 45, 52). Adriamycin levels have been studied by several investigators (1, 52). Benjamin et al. (4, 5) reported that a drug exposure of 94 μg/ml × min...
Chart 2. L1210 cells at a concentration of $1 \times 10^6$/ml were exposed to Adriamycin (2 $\mu$g/ml), BCNU (20 $\mu$g/ml), cis-platinum (platinum) (20 $\mu$g/ml), and vinblastine (0.4 $\mu$g/ml) for differing periods. After drug exposure, cells were incubated in a drug-free environment for 48 hr. After 48 hr, the Cl, as shown in Chart 1, was computed and plotted against the duration of drug exposure. Data are the means. Bars, S.E.

occurred clinically. An 84-$\mu$g/ml $\times$ min Adriamycin exposure produced 50% leukemic cell death of L1210 cells in vitro. Owellen et al. (36, 37) reported that a 20-$\mu$g/ml $\times$ min drug exposure occurred clinically in patients receiving vinblastine. An in vitro drug exposure of 20 $\mu$g/ml $\times$ min was associated with 50% leukemic cell death. The best available data suggested that a drug exposure between 200 and 1200 $\mu$g/ml $\times$ min occurs clinically with BCNU (12, 32, 35, 44). An in vitro BCNU exposure of 500 $\mu$g/ml $\times$ min resulted in 50% cytotoxicity in L1210. For cis-platinum, an exposure of 800 $\mu$g/ml $\times$ min has been reported (10, 31). An in vitro cis-platinum dosage of 640 $\mu$g/ml $\times$ min produced 50% L1210 cell death. The in vitro dosage which produced 50% cell death in the sensitive L1210 tumor line did not conflict with available clinical pharmacokinetic data (Table 1). Measurable cytotoxicity occurred with clinical dose levels in the sensitive L1210 tumor line in an in vitro environment. This measure of cytotoxicity was postulated to be less in resistant neoplasms.

Correlation of in vitro Studies in Animal Models. MOPC 104E murine myeloma, MOS, and L1210 leukemia were studied. The in vivo responsiveness of the 3 tumor models had been determined with conventional cancer treatment criteria. An active agent in vivo is one which reduces tumor surface area or reliable tumor markers by 50% or increases the expected host life span by 30%. While L1210 leukemia was sensitive in vivo to all the agents tested (19), MOPC 104E myeloma was sensitive only to cis-platinum and BCNU (17, 18). The MOS model utilized secretes a circulating tumor cell marker, alkaline phosphatase (21). Treatment with the agents under study was associated with no reduction in marker, no reduction in tumor surface area, and no increase in animal life span. The MOS was therefore, considered to be resistant to the agents studied. The in vitro Cl was 50% for each agent in L1210 leukemia, while in MOPC 104E myeloma BCNU and cis-platinum produced CI's of 80 and 58% respectively. For Adriamycin and vinblastine, the assay in MOPC 104E myeloma showed a CI of 14 and 15%, respectively. In the osteosarcoma model, the CI for all drugs was below 10%. The assay correlated with the animal treatment results. All agents which were active in vivo produced a CI greater than 40%, while all inactive agents produced indices of lesser values ($p = 0.001$; Table 2).

Lymphoma Treatment Results. Seven patients with a diagnosis of malignant non-Hodgkin's lymphoma were studied. While all patients had received prior treatment, none had been treated with any of the agents under study. All antineoplastic therapy was terminated at least 1 month prior to study. Only one antineoplastic drug was administered during a single treatment period. Concurrent steroid therapy was permitted if the patient had received corticosteroids for more than 2 months prior to study. No patient had had prior treatment with either BCNU or Adriamycin. The age range was 42 to 71 years. No patient had a Karnofsky performance score below 80 at the start of therapy. All patients had measurable and progressive disease.

Response criteria were conventional. A partial response was defined as a greater than 50% reduction in measured tumor surface area, unassociated with the development of new lesions and lasting 1 month or longer. Three patients achieved partial remission status. Two patients responded to BCNU, and one patient responded to Adriamycin. No patient experienced complete disappearance of all measurable evidence of disease. There were 8 instances when patients did not respond. Full-dosage drug therapy was continued for 6 weeks before a patient was considered to be a nonresponder.

### Table 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>In vitro drug concentration x time (mg/ml)</th>
<th>Drug concentration x exposure time (mg/ml)</th>
<th>In vitro</th>
<th>In vivo</th>
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<tbody>
<tr>
<td>Adriamycin</td>
<td>42</td>
<td>2.0</td>
<td>84</td>
<td>93 (5)</td>
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<tr>
<td>Vinblastine</td>
<td>51</td>
<td>0.4</td>
<td>20</td>
<td>20 (36)</td>
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<td>cis-Platinum</td>
<td>33</td>
<td>20.0</td>
<td>660</td>
<td>500–1000 (10, 30)</td>
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<tr>
<td>BCNU</td>
<td>25</td>
<td>20.0</td>
<td>500</td>
<td>200–1200 (12, 31, 34, 42)</td>
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### Table 2

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Drug</th>
<th>In vitro cytotoxicity (%)</th>
<th>In vivo antineoplastic activity</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1210</td>
<td>Adriamycin</td>
<td>$50 \pm 5^c$</td>
<td>$+$</td>
<td>$+$</td>
</tr>
<tr>
<td></td>
<td>BCNU</td>
<td>$50 \pm 1$</td>
<td>$+$</td>
<td>$+$</td>
</tr>
<tr>
<td></td>
<td>cis-Platinum</td>
<td>$50 \pm 6$</td>
<td>$+$</td>
<td>$+$</td>
</tr>
<tr>
<td></td>
<td>Vinblastine</td>
<td>$50 \pm 5$</td>
<td>$+$</td>
<td>$+$</td>
</tr>
<tr>
<td>MOPC 104E</td>
<td>Adriamycin</td>
<td>$14 \pm 8$</td>
<td>$-$</td>
<td>$+$</td>
</tr>
<tr>
<td></td>
<td>BCNU</td>
<td>$80 \pm 4$</td>
<td>$+$</td>
<td>$+$</td>
</tr>
<tr>
<td></td>
<td>cis-Platinum</td>
<td>$58 \pm 5$</td>
<td>$+$</td>
<td>$+$</td>
</tr>
<tr>
<td></td>
<td>Vinblastine</td>
<td>$15 \pm 4$</td>
<td>$-$</td>
<td>$+$</td>
</tr>
<tr>
<td>MOS</td>
<td>Adriamycin</td>
<td>$6 \pm 5$</td>
<td>$-$</td>
<td>$+$</td>
</tr>
<tr>
<td></td>
<td>BCNU</td>
<td>$5 \pm 6$</td>
<td>$-$</td>
<td>$+$</td>
</tr>
<tr>
<td></td>
<td>cis-Platinum</td>
<td>$7 \pm 6$</td>
<td>$-$</td>
<td>$+$</td>
</tr>
<tr>
<td></td>
<td>Vinblastine</td>
<td>$0 \pm 6$</td>
<td>$-$</td>
<td>$+$</td>
</tr>
</tbody>
</table>

$^a$ Significant drug activity (+) is associated with a 30% increase in host expected life span, or a 50% reduction of either tumor surface or tumor markers.

$^b$ A positive correlation associated in vitro cytotoxicity of >40% with an active in vivo antineoplastic drug and in vitro cytotoxicity of <40% with an inactive in vivo antineoplastic agent ($p = 0.001$).

$^c$ Mean ± S.E.
Toxicity was predictable and generally mild. Dosage reduction was necessary in only one case, since the patient had extensive marrow involvement and a compromised hematological status. In one patient receiving full-dose BCNU, severe myelosuppression (an absolute granulocyte count below 1000 and resulting sepsis) occurred. There were no drug-associated deaths.

Clinical Correlation of in Vitro Studies. Malignant human tissue was studied before clinical drug therapy was undertaken. All tumor tissue was studied in vitro with each of the 4 drugs. In no instance was there evidence of tumor susceptibility to cis-platinum or vinblastine. In 3 instances, high CI's were recorded. In one instance, this elevation was due to Adriamycin, while in the other 2 instances the elevation was associated with BCNU.

A clinical correlation was demonstrable. The demonstrated 3 instances of in vitro tumor susceptibility were paralleled in the clinical situation by tumor regression with treatment. The 8 demonstrated instances of in vitro tumor resistance correlated with the clinical instance by tumor progression with treatment ($p < 0.01$) (Table 3). There were 7 instances in which in vitro studies demonstrated no activity for vinblastine, which conforms to reports of a lack of disease activity for this drug. No definitive statements could be made regarding a clinical correlation of 7 consecutive negative in vitro studies with cis-platinum. Definitive trial with cis-platinum in the non-Hodgkin's lymphoma group has not been completed. When all tests in animals and humans were combined, a positive correlation was found between in vitro cytotoxicity of >40% and an active antineoplastic agent ($p < 0.00001$) in vivo.

DISCUSSION

Tests predictive of drug activity have been an unrealized cancer research goal for many years. Until recently, it was not possible to treat cancer cells in vitro with a drug dosage resembling the in vivo situation. Recent advances in pharmacology have defined the in vivo pharmacokinetic behavior of many antineoplastic agents, providing a basis for in vivo and in vitro drug dosage comparison. With current concepts in mind, an in vitro dose-response curve was experimentally determined for L1210 leukemia. An in vitro dosage producing measurable cytotoxicity in L1210 leukemia was noted to agree with pharmacological reports of drug level. This experimentally derived dosage was further studied. It was noted that the in vitro cytotoxic effects of this dosage closely paralleled the in vivo antitumor effects in both animals and humans.

While dosage is an obviously critical factor, the mechanism of drug action is also of importance. Over the last decade, it has become apparent that drugs are either cycle specific or cycle nonspecific in their mode of action (27, 46, 47). Suspending tumor cells in tissue culture medium can alter tumor cell kinetics. Altering kinetics may affect tumor sensitivity to cycle-specific agents. Alternatively, sensitive tumors are thought to be susceptible to non-cycle-specific agents regardless of kinetic alterations. These considera-

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient</th>
<th>Drug</th>
<th>In vitro Cl (%)</th>
<th>In vivo treatment result</th>
<th>Correlation</th>
<th>Diagnosis [Rappaport classification (2, 41)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Adriamycin</td>
<td>46 ± 2</td>
<td>PR</td>
<td>+</td>
<td>Poorly differentiated lymphocytic lymphoma, diffuse</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>BCNU</td>
<td>46 ± 3</td>
<td>PR</td>
<td>+</td>
<td>Poorly differentiated lymphocytic lymphoma, nodular</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>Adriamycin</td>
<td>4 ± 2</td>
<td>NR</td>
<td>+</td>
<td>Poorly differentiated lymphocytic lymphoma, nodular, with transformation to diffuse histiocytic lymphoma</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>BCNU</td>
<td>42 ± 2</td>
<td>PR</td>
<td>+</td>
<td>Poorly differentiated lymphocytic lymphoma, diffuse</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>Adriamycin</td>
<td>22 ± 2</td>
<td>NR</td>
<td>+</td>
<td>Well-differentiated lymphocytic lymphoma, diffuse</td>
</tr>
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<td>6</td>
<td>4</td>
<td>BCNU</td>
<td>36 ± 2</td>
<td>NR</td>
<td>+</td>
<td>Well-differentiated lymphocytic lymphoma, diffuse</td>
</tr>
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<td>7</td>
<td>5</td>
<td>Adriamycin</td>
<td>0 ± 1</td>
<td>NR</td>
<td>+</td>
<td>Poorly differentiated lymphocytic lymphoma, diffuse</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>BCNU</td>
<td>14 ± 6</td>
<td>NR</td>
<td>+</td>
<td>Poorly differentiated lymphocytic lymphoma, diffuse</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td>Adriamycin</td>
<td>0 ± 4</td>
<td>NR</td>
<td>+</td>
<td>Well-differentiated lymphocytic lymphoma, diffuse</td>
</tr>
<tr>
<td>10</td>
<td>6</td>
<td>BCNU</td>
<td>19 ± 5</td>
<td>NR</td>
<td>+</td>
<td>Poorly differentiated lymphocytic lymphoma, diffuse</td>
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<tr>
<td>11</td>
<td>7</td>
<td>BCNU</td>
<td>18 ± 4</td>
<td>NR</td>
<td>+</td>
<td>Poorly differentiated lymphocytic lymphoma, diffuse</td>
</tr>
</tbody>
</table>

* A positive correlation associated in vitro cytotoxicity of >40% with an active in vivo antineoplastic agent and in vitro cytotoxicity of <40% with an inactive in vivo antineoplastic agent ($p < 0.01$).

* Mean ± S.E.

* PR, partial remission (a 50% or greater reduction in measured tumor surface area, unassociated with the development of new lesions, lasting 1 month or longer); NR, no remission (a patient not meeting partial response criteria).
tions suggest that in vitro drug treatment would correspond to the in vivo situation if: (a) the studied drug is cycle nonspecific in action; (b) the in vivo and in vitro drug dosages are equivalent; (c) the studied drug does not have a metabolite more active than the parent compound, and (d) the in vivo and in vitro treatment end points are similar.

An optimal in vitro method of predicting in vivo drug effects has not been clearly defined. Trypan blue dye uptake by a cell is considered by some to be an indication of cell death (23, 39, 40). In vitro pharmacological doses of cycle-nonspecific drugs resulted in tumor cell death as measured by trypan blue. Under the in vitro experimentally derived treatment conditions, cells from in vivo sensitive tumors took up trypan blue in greater numbers than did cells from in vivo resistant neoplasms. These results suggested that tumor cell susceptibility might be detectable with this approach.

A clonogenic assay recently has been reported to be capable of measuring tumor cell susceptibility in vitro. This recent development has, in contrast to our technique, the advantage of being predictive for both cycle-specific and cycle-nonspecific agents. A limitation inherent in all clonogenic assays was pointed out by Salmon et al. (44) in their description of this approach. "Logistic and time constraints of this assay may present major problems." (43). Dickson and Suzanger (13) in an earlier publication stated, "The present results indicate that it is possible to select in vitro cytotoxic drugs that inhibit ... human cancer ... no method of predictive testing has gained general acceptance. We believe this reflects the complexities inherent in such testing." Our approach involves a minimum of inherent complexities, essentially no time constraints, and few logistic problems. These advantages, coupled with the positive nature of our findings, suggest that the approach described in this study may have some utility.

In summary, an in vitro predictive test for 4 antineoplastic agents has been described, and preliminary testing has been performed. This test correlates with (a) in vivo drug levels, (b) in vivo response to treatment in animal tumor models, and (c) in vivo response to treatment in humans. These observations suggest a methodological approach to predict the in vivo drug-tumor interaction of cycle-nonspecific drugs under laboratory conditions.

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