ABSTRACT

In a European joint project carried out in 6 laboratories a disease-oriented program was set up consisting of a panel of 7 tumor types, each represented by 4 to 8 different human tumor lines, for secondary screening of promising anticancer drugs. Human tumor lines were selected on the basis of differences in histology, growth rate, and sensitivity to conventional cytostatic agents. Xenografts were grown s.c. in nude mice, and treatment was started when tumors reached a mean diameter of 6 mm in groups of mice where at least 6 tumors were evaluable. Drugs were given at the maximum tolerated dose. For evaluation of drug efficacy, median tumor growth curves were drawn, and specific growth delay and treated/control X 100% were calculated. Doxorubicin (8 mg/kg i.v. days 1 and 8) was effective (treated/control < 50%, and specific growth delay > 1.0) in 0 of 2 breast cancers, 1 of 3 colorectal cancers, 2 of 5 head and neck cancers, 3 of 6 non-small cell lung cancers, 4 of 6 small cell lung cancers, 0 of 3 melanomas, and 3 of 6 ovarian cancer lines. Amsacrine (8 mg/kg i.v. days 1 and 8) was not effective, while dactinomycin (35 mg/kg i.p. days 1 and 8) was active against 2 of 6 small cell lung cancer lines. Brequinar sodium (50 mg/kg i.p. days 1–5) showed efficacy in 4 of 5 head and neck cancers, 5 of 8 non-small cell lung cancers, and 4 of 5 small cell lung cancer lines. The project has been shown to be a feasible approach. Clinical activity for doxorubicin and inactivity for amsacrine against solid tumor types was confirmed in the human tumor xenograft panel. Additional anticancer drugs will be studied in the European joint project to further define the reliability of this novel, promising screening approach.

INTRODUCTION

Since 1985 the screening program for new anticancer drugs used by the American National Cancer Institute has been the subject for discussions on improving drug discovery (1). Up to 1985, the screening system had consisted of the in vivo P388 murine leukemia prescreen and a secondary screen formed by a panel of 5 or 6 murine tumor models and 3 human tumor xenografts. Compounds without minimal activity in P388 leukemia alone as a prescreen would limit the potential to consider the use of human tumor xenografts grown s.c. in nude mice to be an excellent means of generating supplementary data on the potential activity of a promising compound in specified human solid tumors (7).

In Europe, several investigators have gained experience in the establishment of human tumor lines from tumor tissue obtained from patients, the characterization of these lines, and the determination of sensitivity to both conventional and investigational anticancer drugs (8). Human tumor xenografts do not only retain the histological, biochemical, and antigenic characteristics but also the chemosensitivity of the tumor tissue of origin (9–13). Moreover, human tumor lines representing a particular tumor type have the capacity to identify compounds with clinical activity in that disease (14). In 1988, a European multicenter collaboration was created to assess the feasibility and the reliability of “preclinical” phase II studies in a large number of human tumor xenografts (15). We now report on the first results of this joint project in which doxorubicin, amsacrine, brequanin sodium, and dactinomycin were studied in a panel of human tumor lines representing 7 tumor types.

MATERIALS AND METHODS

Animals. Participants in the joint project used female nude mice of a strain available in their laboratories, NMRI nu/nu (E. B., D. P. B., B. J. M. B., H. H. F.), BALB/c nu/nu (M. P. D., Ø. F.), or nude of a mixed background (S. L.). The animals were maintained in cages in isolation under sterile conditions and fed ad libitum. Animal handling was carried out under sterile conditions by a limited number of persons either in laminar flow hoods or within isolators.

Tumor Lines. A selection was made from a large pool of human tumor lines suitable for chemotherapy studies. The criteria for the selection were based on differences in histology, growth rate, and sensitivity to conventional cytostatic agents and will be described in a separate report. The panel was composed of a choice of 7 tumor types which were represented by 4 to 8 different human tumor lines (Table 1).
Phase II Screening in Human Tumor Xenografts

Table 1 Characteristics of human tumor lines grown s.c. in nude mice

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</tr>
<tr>
<td>CXF 280</td>
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</tr>
<tr>
<td>Head and neck</td>
<td></td>
<td></td>
</tr>
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</tr>
<tr>
<td>FKo</td>
<td>Serous moderately differentiated</td>
<td>8-13</td>
</tr>
</tbody>
</table>

* Tumor doubling time given as the range in days.

Drugs. Doxorubicin (commercially available from Farmitalia) as a solution of 10 mg/ml in distilled water was injected i.v. at a dose of 8 mg/kg on days 1 and 8. Amsacrine (provided by Warner Lambert, Hoofddorp, the Netherlands) in a 50 mg/ml solution was further diluted in L-lactic acid to a concentration of 5 mg/ml. At the day of administration a 1-mg/ml solution was made by adding 5% glucose, and injections were given i.v. at a dose of 8 mg/kg on days 1 and 8. Brequinar sodium (NSC 368390; provided by DuPont de Nemours International, Geneva, Switzerland) was dissolved in water at a concentration of 10 mg/ml and further diluted in 0.9% NaCl to 2 mg/ml. Injections were given i.p. at a dose of 50 mg/kg on days 1–5. Datelliptium hydrochloride (SR 95156B; provided by Sanofi Recherche, Montpellier, France) as a solution of 10 mg/ml in water was given i.p. at a dose of 30–35 mg/kg on days 1 and 8.

Treatment. Animals were implanted s.c. in both flanks with 2–3-mm diameter fragments obtained from established human tumor xenografts. Tumor growth was assessed weekly by caliper measurements of the tumor in two dimensions. For tumor lines with a volume doubling time <5 days these measurements were carried out twice weekly. At each day of measurement animal weights were recorded. Treatment was started at the time tumors had reached a mean diameter of 6 mm. The number of mice per treatment per control group had to be sufficient to yield at least 6 evaluable tumors.

Evaluation. Tumor volume was calculated according to the formula

\[ V(t) = 0.5 \times \text{length} \times \text{width} \times \text{width} \]

The increase in tumor volume from the start of treatment \( (V_0) \) until the value at any given time \( (V) \) was calculated for each tumor and day of measurement and expressed as the relative tumor volume \( (V/V_0) \). The median of these values for all evaluable tumors in the control and the treated groups was used to calculate treatment efficacy. Complete remissions were recorded separately and represent tumors that disappeared for a period of at least 4 weeks. Tumors that had not reached 4 mm in one diameter at the start of treatment were considered unevaluable. Animal deaths occurring within 2 weeks after the final drug injection were considered toxic and were excluded from the evaluation.

Three evaluation criteria were used in parallel to express treatment efficacy: (a) median tumor growth curves; (b) specific growth delay over one and two doubling times; (c) the optimal growth inhibition (T/C%) at a particular day within 4 weeks after the last drug administration. To calculate SGD, the end point of evaluation was taken at a median relative tumor volume of twice and 4 times the treatment size from day 0 for control and treated tumors according to the formula (15)

\[ \frac{T_{treatment} - T_{control}}{T_{control}} \]

For the T/C% calculations, the lowest ratio was taken of the median relative volume of treated tumors over that of control tumors multiplied by 100% (15).

Central data evaluation was performed under the responsibility of Drs. Berger and Fiebig, using software specifically designed for the evaluation of nude mouse-human tumor experiments. A growth curve was calculated on the basis of tumor volume experiments for each study group and tumor line. Data were processed on a Sperry Univac 1100/82, for which the software was designed with the use of Fortran 77.

Results

The schedules of doxorubicin and amsacrine were derived from the treatment regimens in solid tumors in the clinic (16, 17). Clinical cycles of 3–4 weeks were converted to weekly cycles x 2. As daily administration for brequinar sodium was required, the drug was administered i.p. on days 1–5. For datelliptium the weekly schedule was selected. Because this drug caused acute toxicity at a dose of 30 mg/kg i.v., experiments were carried out using the i.p. approach. The maximum tolerated dose for all four drugs was determined in non-tumor-bearing mice first by Dr. Boven. This dose was based on a median weight loss of 10% in mice in the week following the first injection. In the ultimate experiments some variation was evident for the effect of a particular drug on weight loss for the various mouse strains in the six laboratories. This effect was most pronounced for doxorubicin. When this occurred, excessive weight loss or toxic deaths compromised the evaluaiblity of the experiments. Delayed toxicity resulting in late deaths has not been observed with any of the drugs.

The treatment results of the various experiments obtained with the four drugs in the human tumor lines are presented in Tables 2-5. In each of the tables the following variables are given per tumor line: (a) the number of evaluable tumors; (b) the maximum median decrease in body weight for evaluable animals as compared to the body weight at the start of treatment (%); (c) the number of animals dead from toxicity.

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The abbreviations used are: T/C, treated/control; SGD, specific growth delay; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer.
### Table 2: Activity of doxorubicin, 8 mg/kg i.v. on days 1 and 8, in human tumor lines

<table>
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<tr>
<th>Tumor line</th>
<th>No. of evaluable tumors</th>
<th>Maximum BWC a (%)</th>
<th>No. of toxic deaths</th>
<th>Optimal T/C</th>
<th>SGD</th>
<th>Evaluability?</th>
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<td></td>
<td></td>
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<td>31</td>
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* BWC, body weight change; NA, not available; NR, volume 400% not reached.
* Only five tumors evaluable; six others too small at the start of treatment.

Within 14 days after the last drug administration; (d) the optimal treatment result expressed as median relative tumor volume as compared to control and the day of measurement; (e) the SGD related to one (100–200 mm³) and two (100–400 mm³) tumor volume doubling times; (f) the evaluability of each experiment.

In Table 6 a summary is given for the responding tumor lines of the seven tumor types to each of the four drugs tested. Based on the experience of the participating investigators, a T/C <50% or a SGD >1.0 were considered minimum values for antitumor activity. When the results were reviewed it was decided that combining both evaluation criteria would reflect the best drug efficacy.

A total of 35 human tumor lines were tested for sensitivity to doxorubicin. Line LXF 605 was included in the evaluation because the excessive weight loss of 23% appeared to be partly attributable to tumor response, and all animals survived beyond day 21. In tumor types known to be clinically responsive doxorubicin showed activity in 0 of 2 breast cancer lines, 4 of 6 SCLC lines, and 3 of 6 ovarian cancer lines. In addition, in 3 of 6 NSCLC lines doxorubicin was active as well as in 1 of 3 of the colorectal cancer lines and in 2 of 5 of the head and neck cancer lines. In melanoma, a tumor type not responsive to doxorubicin, none of the lines responded to the drug. A T/C <25% and a SGD >2.0 were obtained in the HNX-HEp-2 head and neck cancer line, the LXF 529 NSCLC line, and the four SCLC lines LXBOS, LXF 538, LXF 605, and LXF 650.

Amsacrine was investigated in 33 human tumor lines, of which 30 were considered evaluable. Except for CXF 233 and LXF 409, no major body weight change was observed. This might suggest that amsacrine was tested at a suboptimal dose. It should be noted that amsacrine was diluted for this study as indicated on the instruction leaflet for clinical use. This limited the maximum dose to 8 mg/kg (0.24 ml i.v. in a 30-g mouse). However, at a dose of 10 mg/kg i.p. in LXF 605-bearing mice, 3 of 6 animals did not survive day 17, and the antitumor effect induced by amsacrine was not improved. In view of the low level of overall activity of this drug, it is improbable that significant activity would be reached with the optimal dose in other tumor lines.
Of 35 human tumor lines studied for sensitivity to brequinar sodium, 33 were considered evaluable. The drug appeared specifically active in tumor lines of head and neck cancer, NSCLC, and SCLC with, respectively, 4 of 5 lines, 5 of 8 lines, and 4 of 5 lines responding.

The fourth compound studied, datelliptium, could be evaluated in 34 of 35 human tumor lines. In three lines the drug induced a body weight change > —15%. Since no animal death occurred and the lines were not responsive to datelliptium, the experiments were considered evaluable. In only two SCLC lines, LXFL 529 large cell NSCLC line was responsive to all drugs studied. The SCLC line LXFS 605 was responsive to doxorubicin and brequinar sodium. In those lines responding to brequinar sodium significant growth inhibition (T/C <50%) was mainly observed between days 7 and 14 (Table 4), while the optimal T/C% for doxorubicin was usually reached after day 14 (Table 2).

DISCUSSION
Since 1988, several discussions have taken place between the investigators of this European joint project on the design of phase II drug screening in human tumor xenografts. General consent was obtained on the tumor types to be studied, the main type, and the number of lines per tumor type. Agreement was reached on the size and the number of xenografts at the start of treatment, the measurement of tumors, and the evaluation of the experiments (15). In the first step it was decided to include four anticancer drugs, i.e., doxorubicin as a drug known to be active in a variety of human solid tumors in the clinic, amsacrine as an inactive drug in these malignancies, the investigational compound brequinar sodium that had just entered phase I clinical trials, and datelliptium, which was still in the preclinical phase of drug development. Maximum tolerated

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<th>No. of toxic deaths</th>
<th>Optimal T/C %</th>
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* BWC, body weight change; NA, not available.
* Only five tumors evaluable; three others too small at the start of treatment.
* Only five tumors evaluable; one other measurement on day 0 only missing.
### Table 4 Activity of brequinar sodium, 50 mg/kg i.p. on days 1–5, in human tumor lines

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*a BWC, body weight change; NA, not available.
*b Test done at 60 mg/kg i/p. 1, 2, 3, 4, and 5.

dose studies carried out in one laboratory appeared to be adaptable in other laboratories housing nude mice of other strains. In practice, only a few of the experiments had to be discarded, and this was due mainly to reasons of drug toxicity. However, one should keep in mind that body weight change may also be influenced by the effect of the xenograft on the host. As an example, median body weight change in the six human ovarian cancer lines studied in the same strain of mice in the same laboratory varied between —2% and —10% after doxorubicin treatment.

Since the feasibility of this joint project appears to be well proven, the question arises as to whether this in vivo screening system generates reliable data. Therefore, the reference agents doxorubicin and amsacrine were included. In the clinic, doxorubicin shows the greatest efficacy in hematological malignancies, breast cancer, ovarian cancer, sarcomas, and SCLC (16). Several other tumor types are known to be occasionally responsive, such as NSCLC and head and neck cancer. In this respect, the overall sensitivity of our human tumor xenograft panel was remarkably reflective of the clinical data of doxorubicin. In cancer patients, amsacrine is a well-known drug in the treatment of hematological malignancies, with emphasis on acute leukemias, while a variety of phase II trials demonstrated no useful activity against human solid tumors (17). Inactivity against solid tumor types was confirmed in our xenografts, which was further proof of the reliability of the panel.

For brequinar sodium, our panel predicted activity against head and neck cancer, NSCLC, and SCLC. Preclinical analysis of brequinar sodium has shown the drug to be an antimetabolite and enzymes dihydroorotic acid dehydrogenase (18). In vitro, prolonged exposure was necessary for a long-lasting depletion of pyrimidine nucleotides and a substantial suppression of RNA and DNA synthesis. Repletion of all nucleotides by uridine and/or cytidine restored cell growth. In human colon cancer-bearing nude mice, the tumor tissue concentration of radiolabeled brequinar sodium measured approximately 50% of the 1-h peak level at 24 h (19). Thus, one may expect prolonged exposure to the drug in vivo upon daily injections given for 5 days. Indeed, in responsive tumor lines growth inhibition was
Table 5 Activity of datelliptium, 30—35 mg/kg i.p. on days 1 and 8, in human tumor lines

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<th>No. of toxic deaths</th>
<th>Optimal T/C%</th>
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a BWC, body weight change; NA, not available.
b Test done at 30 mg/kg i.p. days 1 and 8.
c 4 of 5 animals survive day 30 without significant weight loss.

Table 6 Therapeutic efficacy of doxorubicin, amsacrine, brequinar sodium, and datelliptium expressed as the number of human tumor lines with a T/C < 50% and/or a SGD > 1.0 of the total number of evaluable lines (n)

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most pronounced in the first 2 weeks of treatment. The mechanism of action also explains rapid regrowth of tumors after discontinuation of drug administration. In the clinic, a number of phase I trials have been carried out (20—22). Mucocutaneous side effects and myelotoxicity were dose-limiting factors. Thus far, phase II studies in solid tumor types have failed to show significant antitumor activity for brequinar sodium. An explanation for the discrepancy in efficacy could possibly be found in a difference between mice and humans for the degree and the duration of uridine depletion in tissues as a result of the inhibition of dihydroorotic acid dehydrogenase (23).

Datelliptium showed low activity in the panel, but in 2 of 6 SCLC lines its activity was significant. Datelliptium is a water-soluble compound belonging to the ellipticine family, a group of
Before general use of the panel we should await further proof that our human tumor xenografts will accurately predict the efficacy of new compounds, thus improving the efficiency of phase II clinical trials. Recognition of the mechanisms underlying possible discrepancies in response between tumor-bearing mice and cancer patients is essential for a more rational use of the panel (30). In this respect, we are currently extending our experience with another four anticancer drugs, including cisplatin and diaziquone as reference agents.

REFERENCES


PHASE II SCREENING IN HUMAN TUMOR XENOGRAFTS


5947
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