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Effectiveness of Cisplatin, Paclitaxel, and Suramin Against Human Malignant Mesothelioma Xenografts in Athymic Nude Mice

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Background and Objectives: Malignant mesothelioma has a poor prognosis and is refractory to many agents. The antitumor effectiveness of cisplatin, paclitaxel, and suramin as single agents and in combination was evaluated in vivo against four lines of human pleural malignant mesothelioma xenografts in athymic nude mice, including one epithelial type and three fibrosarcomatous.

Methods: After growth of tumors occurred by day 54 or 55, mice were randomized in groups of four each to receive either cisplatin 4 mg/kg intraperitoneally weekly ×5, or paclitaxel (Taxol) 12.5 mg/kg subcutaneously daily 5 days/week for 3 consecutive weeks, or suramin 60 mg/kg intraperitoneally daily ×4,versus controls treated with normal saline.

Results: Cisplatin was very effective against one line and also to a lesser degree against another line. Paclitaxel showed antitumor effects similar to cisplatin, being very effective in one line, and also showed good activity in another line. Suramin was basically inactive in all four lines. Following the results obtained with these single agents, it was decided to evaluate the combination of cisplatin and paclitaxel, which resulted in more pronounced antitumor effect in all four cell lines.

Conclusions: These results indicate that the combination of cisplatin and paclitaxel is superior to each agent alone in this model, and that it deserves to be evaluated in patients with malignant mesothelioma.

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KEY WORDS: **malignant mesothelioma; nude mouse; cisplatin; paclitaxel; suramin**

INTRODUCTION

Malignant mesothelioma (MM) is a disease of growing importance. Its incidence has been increasing in the past decades, largely because of past exposure to asbestos, its major etiologic agent [1]. It is estimated that about 27 million workers have been exposed to asbestos from 1940 to 1979 in the United States alone, leading to a calculated annual death rate from MM of about 2,000 in 1980, and up to 3,000 for the late 1990s [2]. Neither surgery nor radiotherapy have any curative potential for MM, and the disease is refractory to most chemotherapeutic agents. Median survival from diagnosis is about 1 year.

Efficacy of many chemotherapeutic agents in patients with MM is difficult to assess in this still uncommon

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neoplasm. Since 1978, we have established at Mount Sinai a laboratory model for this disease by transplanting human MM specimens into nude mice [3]. This model enabled us to identify some effective regimens for this tumor, such as the combination of cisplatin and mitomycin [4], and the increased antitumor effect of chemotherapy by human recombinant interferon-α (IFN-α [5]. Results of chemotherapy studies in this nude mouse model have correlated well with clinical experience [6–8].

It was recently shown that suramin has been effective when tested in vitro against six human MM cell lines, with inhibition of ^{3}H-thymidine incorporation of 31–96% at concentrations of 300 μg/ml, which are achievable in vivo [9]. There was, however, no inhibition of ^{3}H-leucine incorporation, leading the authors to suggest a cytostatic rather than cytotoxic effect. It was therefore important to study the effectiveness of suramin against our MM xenografts in nude mice. Suramin is known to interact with the binding of growth factors, such as PDGF, to cell surface receptors [10,11]. Since platelet-derived growth factor (PDGF) has been shown to be an autocrine growth factor for MM [1], there was further justification to explore the activity of suramin against MM.

Paclitaxel (Taxol) is the first representative of a new class of antitumor agents, the taxanes, and is now widely used in the treatment of many forms of cancer, including ovarian, breast, and lung cancers [12]. It has a unique action at the level of the microtubules, which become stable and dysfunctional, causing cell death. Because of its unique mechanism of action and its wide spectrum of activity, it was elected to also test paclitaxel in the present model to assess its efficacy against MM, a disease for which clinical data of its activity were lacking or were at a very preliminary stage.

In the current investigation, we evaluated the role of two new agents, Taxol (paclitaxel) and suramin, compared to an established agent, cisplatin, against four lines of human MM s.c. xenografts in nude mice established from patients with histologically confirmed pleural MM.

MATERIALS AND METHODS

Mice

In this study, 4- to -6-week-old female nu/nu homozygous (nude) mice were obtained from the Charles River Breeding Laboratory, through the National Cancer Institute (Bethesda, MD). The mice were maintained under aseptic conditions, which include filtered air and sterilized food, water, bedding, and cages. Experiments began after observing the mice for 2 weeks for possible signs of infection.

Tumor Xenografts

Three lines (MMPC-2, MMPC-3, and MMPC-4) were obtained from three patients with fibrosarcomatous pleural MM (or mixed sarcomatous/epithelial but predominantly sarcomatous MM with very few epithelial areas) , whereas the fourth one (MMPC-1) was from a patient with epithelial pleural MM. Tumor tissues were obtained at surgery and immediately processed for transplantation in nude mice. The histologic diagnosis of pleural MM was established in all four patients by surgical pleural biopsy. Case MMPC-1 was previously reported (as Line 5) [13] and was purely epithelial (tubulopapillary), special stains were positive for hyaluronic acid, weakly positive for cytokeratin, negative for mucin and carcinoembryonic antigen, and the diagnosis of MM was also confirmed by electron microscopy. Case MMPC-2 was a sarcomatous MM with very few nests of epithelial tumor, and was cytokeratin positive. Case MMPC-3 was also sarcomatous with very few areas of epithelial tumor negative for mucin. Case MMPC-4 was purely sarcomatous and electron microscopy confirmed the diagnosis of mesothelioma.

Transplantation was carried out as previously described (3,4) using sterile conditions under a fiberglass tissue hood (Fisher Scientific, Pittsburgh, PA). The tumors were chopped into 1- to 2mm cubes after excision of adipose and necrotic tissues, and were placed s.c. in one site in the right axillary area of each mouse using a trocar.

Treatment Agents

After growth of tumors occurred by day 54–55 after implantation, mice were randomized in groups of four each to receive either cisplatin (Bristol-Myers-Squibb, Princeton, NJ), 4 mg/kg intraperitoneally (i.p.) weekly ×5, or paclitaxel (Taxol, Bristol-Myers-Squibb, Princeton, NJ) 12.5 mg/kg subcutaneously (s.c.) daily 5 days/week for 3 consecutive weeks, or suramin 60 mg/kg i.p. daily ×4, versus controls treated with normal saline 0.2 ml i.p. weekly ×4. In addition, another group of mice received the combination of Taxol + cisplatin at the same doses and schedule as above, with both drugs starting on the same day. All the experimental treatments were carried out simultaneously. Cisplatin and paclitaxel were obtained commercially, whereas suramin was a generous gift from Dr. Cy Stein (Columbia University, New York, NY). The dose of cisplatin was identical to the one used in our prior experiments [5], where we compared the acute toxicity of cisplatin in nude mice with mesothelioma xenografts when given at three dose levels (10 mg/kg, 6 mg/kg, and 4 mg/kg) given i.p. weekly for 3 weeks. The 10-mg/kg and 6-mg/kg unit doses were too toxic and produced acute deaths or major weight loss in more than 50% of animals. We therefore selected a unit dose of cisplatin of 4 mg/kg, which had acceptable toxicity (<25% mortality in our original experiments), and which can be given weekly for up to 5 weeks. The dose and route of administration of paclitaxel were selected ac-

cording to studies in nude mice by Riondel et al. [14]. These authors conducted acute toxicity studies of paclitaxel in nude mice and selected the unit dose of 12.5 mg/kg daily, being 1/20th of the LD_{50} dose (lethal dose for 50% of animals). They gave paclitaxel subcutaneously at the schedule used in the current study and observed good antitumor effects in mice with various human tumor xenografts with acceptable toxicity limited to slight weight loss and no acute mortality. The dose of suramin was indicated by Dr. C. Stein (personal communication).

Analysis of Activity

The mice were weighed weekly and the s.c. tumors measured twice a week using a caliper. Tumor volumes (V) were calculated using the formula for a prolate ellipsoid:

$$V = (\pi/6)\ LW^2$$

where L is the longest diameter and W the width along the perpendicular axis [15]. Measurements were carried out weekly from the first day of observed tumor growth after transplant to the time the mouse died or its tumor became necrotic or too large, whichever came first. Two methods were used to evaluate the efficacy of these treatments. The conventional method, described by Geran et al., compares the final tumor volumes in the treated arms T to those in the control arm C (ratio T/C), with a value of <0.42 indicating activity [15]. The point in time at which the tumor volumes were compared was selected to allow optimum comparison of tumor volumes in treated animals compared to control animals, before tumors become necrotic. It varied within a narrow range for the four lines, from day 89 post-transplant in line MMPC-4 to day 110 for lines MMPC-1, MMPC-2, and MMPC-3.

The other method uses the average total tumor volume (ATTV) which was calculated by taking the area under the curve (i.e., the integral) of the tumor volumes over time for each mouse. This ATTV represents the average height of the volume-time curve throughout the study, thereby giving an overall index of tumor size. A nonparametric analogue of the one-way analysis of variance (ANOVA) was used to compare the ATTVs of the mice in all treatment arms to determine overall significance. The Kruskal-Wallis method was used for this analysis because of the small sample sizes. Based upon the determination of overall significance, multiple pairwise comparisons were then carried out between treatment arms [16].

RESULTS

Figures 1–4 depict the volumes of the tumors over time for all four human MM cell lines in nude mice. Each point on the curve represents the mean tumor volume for all mice in a treatment arm, and bars indicate standard error (SE). In Figure 1, cisplatin alone and paclitaxel alone produced identical antitumor effects, and the corresponding tumor growth curves are therefore superimposed. Treatment arms were well tolerated and only two early deaths (both at day 60 after transplant) were observed, including one control animal and one treated with suramin.

Using the T/C method, the results shown in Table I indicate that the activity of suramin did not reach the threshold level of 0.42 in any of the four human MM lines. Suramin was totally ineffective in line MMPC-3, and provided at best minor slowing of tumor growth in the other three lines. Its activity was greatest in line MMPC-2, with a T/C = 0.48, close to the threshold of 0.42. Cisplatin was most effective in line MMPC-1 (T/C = 0.14), and to a lesser degree in line MMPC-4 (T/C = 0.30). Its activity in the other two lines was borderline, with T/C = 0.46 for MMPC-2 and 0.47 for MMPC-3. Paclitaxel was also most effective against line MMPC-1, with T/C = 0.14 and an antitumor activity very similar to cisplatin (Fig. 1). Paclitaxel was also active against MMPC-2 (T/C = 0.32), where it showed a slightly higher antitumor effect than cisplatin, especially after day 95 (Fig. 2). Opposite effects were observed in line MMPC-4 (see Fig. 4), where paclitaxel was slightly less effective than cisplatin, with a borderline T/C of 0.41. On the other hand, paclitaxel was ineffective against line MMPC-3 (T/C = 0.81) (Fig. 3).

The most effective treatment arm was the combination of cisplatin and paclitaxel. It showed activity against all four lines, with T/C = 0.04 for MMPC-1, 0.10 for MMPC-2, 0.19 for MMPC-4, and 0.21 for MMPC-3.

Comparisons were also made for the activity of the cisplatin + paclitaxel arm compared to either agent alone using the T/C method. (Table II). The combination was better than either single agent in all four lines. This effect was most apparent in lines MMPC-1 and MMPC-2, but was also observed in line MMPC-3, where it was clearly better than paclitaxel (T/C = 0.25), but only slightly more effective than cisplatin (T/C = 0.44). Results with the combination in line MMPC-4 showed somewhat opposite results. Tumor growth inhibition by the combination was also increased compared to either agent alone in line MMPC-4 (Fig. 4), but to a lesser extent, with T/C = 0.46 when compared to paclitaxel alone, and 0.63 when compared to cisplatin alone.

Table III shows the median ATTVs for each treatment arm. Statistical analysis of ATTVs was conducted using the Kruskal-Wallis test followed by multiple pairwise comparisons between treatment arms. Since there was a total of five treatment arms per line, there were ten possible pairwise comparisons of these groups. In order to maintain an overall significance level of 0.05, each pair-

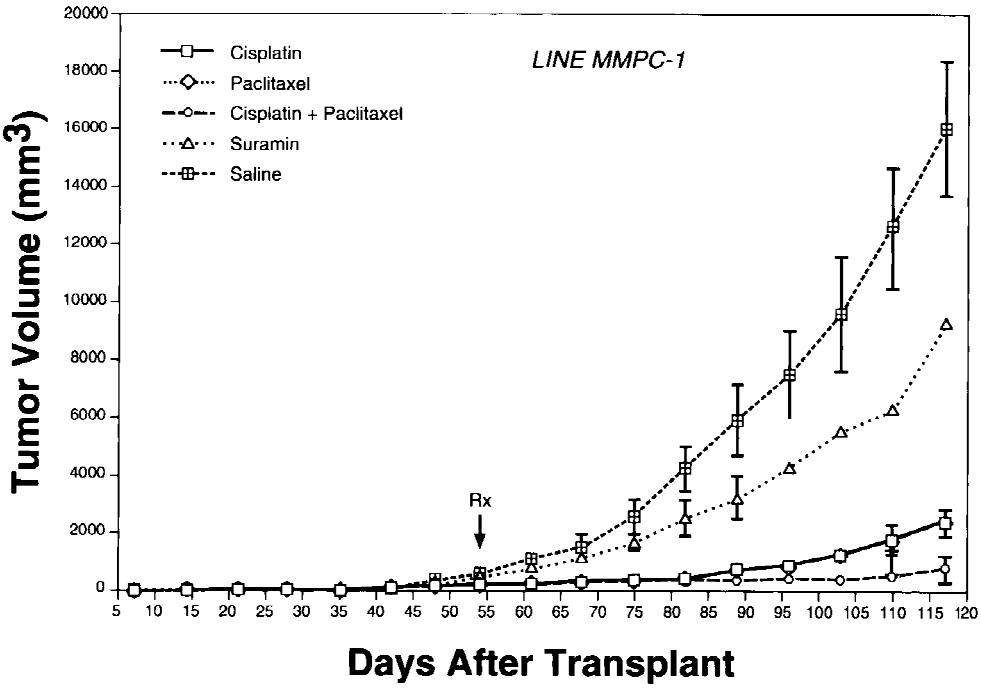

Fig. 1. Line MMPC-1. Growth curves of human mesothelioma xenografts in nude mice. All treatments (Rx, arrow) were started on day 54 after tumor transplant. See text for doses and schedule. Each treatment group includes four mice with one subcutaneous xenograft each. Points, mean tumor volume; bars, standard error of the mean tumor volume. In this line, growth curves after cisplatin alone and paclitaxel alone are superimposed.

TABLE I. Overall Results of Antitumor Activity Using the T/C Method*

	T/C per line			
Treatment arm[a]	MMPC-1	MMPC-2	MMPC-3	MMPC-4
Suramin	0.56	0.48	1.00	0.55
Cisplatin	0.14	0.46	0.47	0.30
Paclitaxel	0.14	0.32	0.81	0.41
Cisplatin + paclitaxel	0.04	0.10	0.21	0.19

*Ratio of mean tumor volume of treated animals over controls measured day 82–110 after tumor transplant. A ratio T/C <0.42 indicates activity (15).

[a]Treatment administered on day 54 or 55 after tumor transplant. See text for dose and schedule.

wise comparison was therefore run at the 0.005 level of significance. Significant results for treatment arms compared to controls included cisplatin+paclitaxel for line MMPC-1 ($P = 0.0036$), line MMPC-3 ($P = 0.0042$), and line MMPC-4 ($P = 0.0036$). Failure to exhibit significance at the 0.005 level for other effective treatments as defined by the T/C method was attributed to the small sample size involved in these experiments. For instance, comparison of cisplatin versus controls reached a *P*-value of 0.0086 for line MMPC-1, and comparison of paclitaxel versus controls yielded a p value of 0.0232 for line MMPC-4.

In order to determine if tumor growth rates correlated with response, the tumor volumes at day 48 after tumor transplant (one week before treatments) were calculated for each treatment group (Table IV). The fastest growth rates were seen in lines MMPC-4 and MMPC-3, followed by MMPC-1 and MMPC-2. There was no correlation between growth rate and tumor response.

DISCUSSION

Since our first successful transplantation of human MM specimens into nude mice as reported in 1980 [3], our approach to find effective treatments for this refractory neoplasm has been based on clinical correlations using the therapies that achieved the best results in this experimental model.

The combination of mitomycin and cisplatin was the first effective treatment found in nude mice [4]. Our initial pilot clinical trial of this combination in 12 patients with MM yielded four objective responses (one complete and three partial) [4]. A direct patient-xenograft comparison was also seen in a patient with pleural MM, in whom complete clinical response to mitomycin and cisplatin correlated with experimental results in nude mice carrying xenografts obtained from that patient [6]. The combination of mitomycin and cisplatin was also active in a randomized phase II trial conducted by the Cancer and Leukemia Group B, where it showed a 26% response rate in 35 patients with MM (including two complete responses), whereas the combination of doxorubicin and cisplatin yielded a 14% response rate, with no complete response, in another group of 35 patients with MM [17]. The use of mitomycin and cisplatin has also been com-

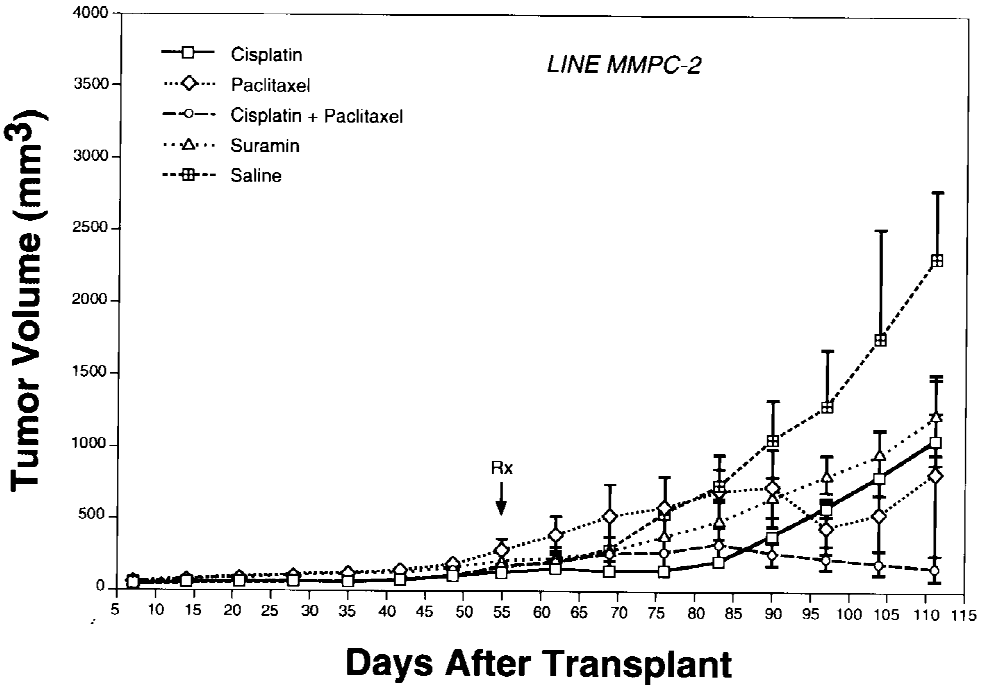

Fig. 2. Line MMPC-2. Growth curves of human mesothelioma xenografts in nude mice. All treatments (Rx, arrow) were started on day 55 after tumor transplant. See text for doses and schedule. Each treatment group includes four mice with one subcutaneous xenograft each. Points, mean tumor volume; bars, standard error of the mean tumor volume.

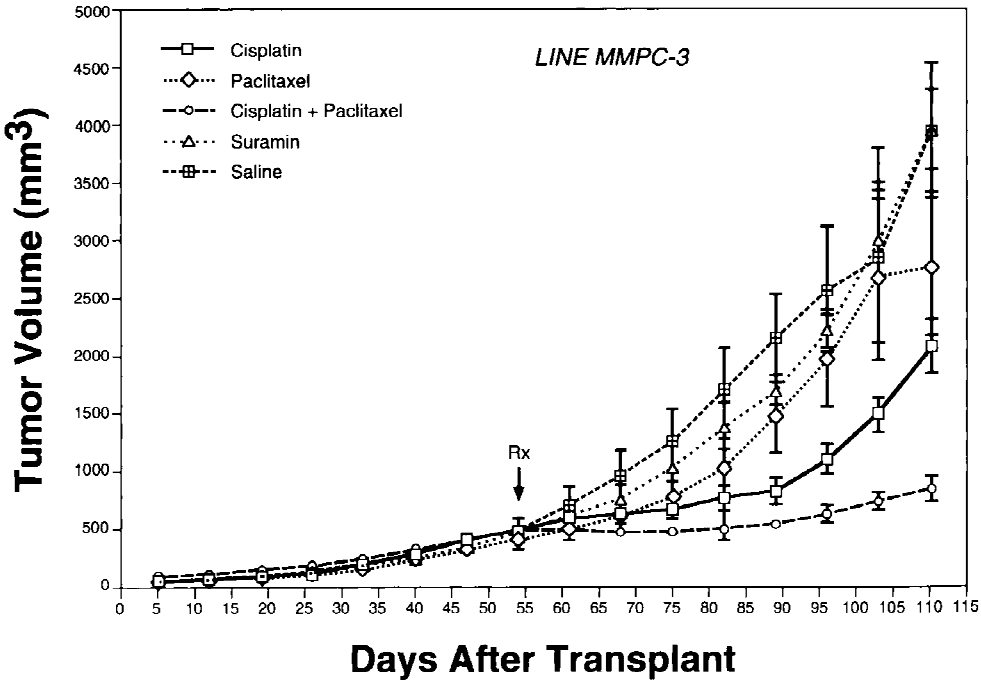

Fig. 3. Line MMPC-3. Growth curves of human mesothelioma xenografts in nude mice. All treatments (Rx, arrow) were started on day 54 after tumor transplant. See text for doses and schedule. Each treatment group includes four mice with one subcutaneous xenograft each. Points, mean tumor volume; bars, standard error of the mean tumor volume.

bined with the surgical treatment of pleural MM (pleurectomy or decortication), given first by intracavitary administration, followed by systemic injection. This approach resulted in a median survival of 17 months in 27 patients at the Memorial Sloan-Kettering Cancer Center [18], and of 13 months in 19 patients treated at the Cleveland Clinic [19]. Similarly, patients with peritoneal MM and malignant ascites were treated with intraperitoneal

TABLE II. Antitumor Activity of the Combination of Cisplatin and Paclitaxel Compared to Either Agent Alone Using the T/C Method*

	T/C per line			
Treatment arm	MMPC-1	MMPC-2	MMPC-3	MMPC-4
Combination vs. cisplatin	0.32	0.21	0.44	0.63
Combination vs. paclitaxel	0.32	0.30	0.25	0.46

*Ratio of mean tumor volume of treated animals in the combination arm (cisplatin + paclitaxel) compared to single agent as indicated, measured day 82–110 after tumor transplant.

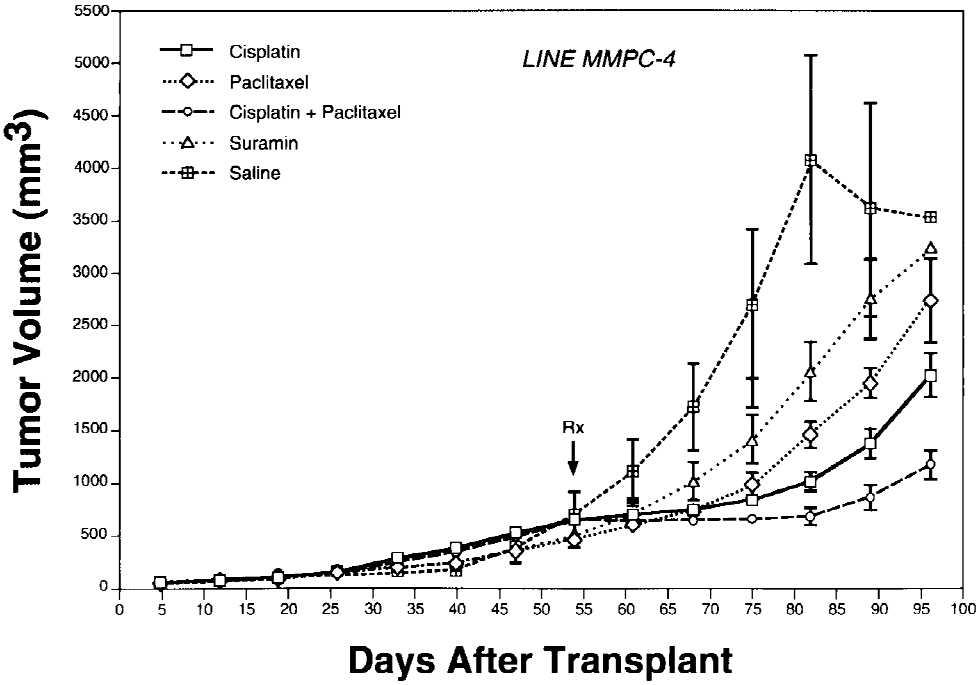

Fig. 4. Line MMPC-4. Growth curves of human mesothelioma xenografts in nude mice. All treatments (Rx, arrow) were started on day 54 after tumor transplant. See text for doses and schedule. Each treatment group includes four mice with one subcutaneous xenograft each. Points, mean tumor volume; bars, standard error of the mean tumor volume.

instillations of mitomycin and cisplatin by Markman and Kelsen [20]. Control of ascites was observed in 7 out of 15 patients (47%), 4 patients survived more than three years, and 2 patients were alive and clinically disease-free more than 5 years following treatment [21].

Our next protocol in nude mice with human MM xenografts was to study the activity of human recombinant IFN-α_{2a} alone and in combination with chemotherapy [5]. Whereas interferon by itself showed minimal antitumor activity in this system, its combination with an effective agent (cisplatin or mitomycin, depending on which MM line) increased the antitumor activity of the chemotherapeutic agent. In vitro sensitivity studies using four human MM cell lines also confirmed that the growth inhibitory effects of chemotherapy drugs were improved by the addition of interferon [22]. In that system, cell lines were consistently sensitive to human IFN-α, but sensitivity to human IFN-Γ was more variable. A phase II trial of human recombinant IFN-α_{2b} in 13 patients with MM yielded 2 partial responses (15%) [23]. The use of human IFN-γ given intrapleurally was effective in patients with early pleural MM, with a response rate of 45% in 29 patients with stage I disease [24]. IFN-α has also been combined with chemotherapy in clinical trials in MM. Its combination at a dose of 3×10^6 U on days 1 to 4 with cisplatin given by an intensive weekly schedule at a dose of 60 mg/m^2 produced a response rate of 40% (10 partial responses among 25 evaluable patients) in a French trial [25]. The combination of IFN-α at a dose of 5×10^6 U/m^2 three times per week with cisplatin also given weekly but at a lower dose (25 mg/m^2) and supplemented with daily tamoxifen resulted in a partial response rate of 21% in 34 patients in a trial by Pass at the National Cancer Institute [26]. These data again support the validity and clinical usefulness of the nude mouse system for MM.

TABLE III. Median Values of Average Total Tumor Volumes per Line†

Treatment arm	MMPC-1	MMPC-2[a]	MMPC-3	MMPC-4
Controls	2,834	383	908	981
Suramin	858	324	701	639
Cisplatin	294	242	493	566
Paclitaxel	341	276	592	492
Cisplatin + paclitaxel	251*	170	378*	466*

†Represents (in mm^3) the median average height of the volume–time curve throughout the study and was obtained by calculating the area under the curve over time for each mouse.
[a]In line MMPC-2, one control animal and one suramin-treated animal were removed from the analysis due to early deaths on day 60 after transplant.
*$P < 0.005$ for combination arm versus control by pairwise comparison.

TABLE IV. Median Values (and Range) of Tumor Volumes (in mm^3) Before Start of Treatment

Treatment arm	Mesothelioma line			
	MMPC-1	MMPC-2	MMPC-3	MMPC-4
Control	289 (107–592)	90 (59–109)	366 (91–456)	400 (62–592)
Cisplatin	116 (57–223)	97 (37–122)	326 (289–464)	464 (418–665)
Paclitaxel	138 (70–254)	171 (130–243)	263 (148–422)	310 (247–436)
Suramin	310 (133–426)	160 (45–183)	301 (225–456)	321 (206–502)
Cisplatin + paclitaxel	197 (145–210)	62 (60–185)	365 (297–442)	477 (392–501)

The current investigation evaluated the activity of two new agents in this system, suramin and paclitaxel. The selection of suramin was based both on theoretical and experimental reasons. Suramin has been shown to block the binding of a range of tumor growth factors, including PDGF [10,11]. The latter is a major growth factor and possibly even an autocrine growth factor for MM [1]. Suramin also inhibits the metabolism of glycosaminoglycans, and lysosomal enzymatic activity of iduronate sulfatase, beta-glucuronidase and hyaluronidase are consistently decreased after suramin treatment [11]. These observations are of interest because MM cells are known to produce hyaluronic acid [1]. Finally in vitro experiments have suggested that suramin is effective against human MM cell lines [9]. Our results with suramin at the dose and schedule used in this report were rather disappointing, and failed to indicate good antitumor activity in this system.

Paclitaxel is a member of a new class of antitumor agents, the taxanes, and has unique cytotoxic effects [12]. It promotes the polymerization of tubulin, whereas other antimicrotubule agents such as vinca alkaloids induce the disassembly of microtubules. It has a very broad spectrum of activity against human tumors, and deserved to be investigated for its activity in MM. The schedule and dose of paclitaxel used in our experiments were directly derived from the report of Riondel et al. [14], who observed activity against a number of human tumor xenografts using this method of administration. The activity of paclitaxel as a single agent against our human MM xenografts was modest, and overall comparable to the activity of cisplatin. Two clinical trials evaluating the activity of paclitaxel in patients with MM have been reported. In the Cancer and Leukemia Group B (CALGB) trial, paclitaxel at a dose of 250 mg/m^2 by 24-hr i.v. infusion resulted in 2 partial responses in 15 patients (13% response rate) [27]. In the European Organization for Research and Treatment of Cancer (EORTC) trial, paclitaxel was given at a dose of 200 mg/m^2 by 3-hr i.v. infusion and produced no major objective responses in 25 patients with pleural mesothelioma [28]. In contrast with these clinical trials, paclitaxel appeared more effective against mesothelioma xenografts in the current investigation, where it showed good antitumor effect in line MMPC-1 (T/C = 0.14), moderate antitumor effect in line MMPC-2 (T/C = 0.32), and borderline activity in line MMPC-4 (T/C = 0.41). Whether these differences between experimental and clinical activities of paclitaxel are due to small numbers (of mice and patients evaluated), to sampling variations, or to the more protracted schedule of paclitaxel in mice cannot be determined at this time.

On the other hand, the combination of paclitaxel and cisplatin has shown good activity in the current work and deserves a clinical trial in patients with MM. It is noteworthy that such a combination was shown to be significantly superior to cyclophosphamide and cisplatin in terms of response rate and survival in patients with advanced ovarian cancer [29]. Preclinical studies of paclitaxel combined with cisplatin showed that such combination resulted in increased cytotoxicity in both in vivo and in vitro systems. When compared to several other doublets of various chemotherapeutic agents combined with paclitaxel in the murine Madison 109 lung carcinoma model, only the combination of paclitaxel and cisplatin showed antitumor activity significantly greater than the maximum effects of the individual drugs [30].

Any experimental model has limitations for clinical extrapolation. It appears, however, that the nude mouse model has generally correlated well with clinical experience. These xenografts usually retain the original human morphological features, and results of chemotherapy in a wide spectrum of tumor types have usually been consistent with clinical experience [31–33]. Direct comparisons between antitumor activity of drugs in patients and in their own xenografts in mice have confirmed this predictive value [33,34]. Doses of chemotherapy in mice can be

approximately extrapolated to human doses by converting them to a mg/m^2 basis [35]. In that respect, the human equivalent doses of chemotherapy used in this work can be estimated to be 12 mg/m^2 weekly for 5 weeks (total dose per course 60 mg/m^2) for cisplatin, 37.5 mg/m^2 for each daily dose of paclitaxel (total dose per course 562.5 mg/m^2), and 180 mg/m^2 daily for suramin (total dose per course 720 mg/m^2). Major drawbacks of the nude mouse model are the high cost of animals and the need for sterile environment, thereby limiting the number of mice which can be evaluated. In that regard, and in view of the large number of treatment arms to be conducted simultaneously, the number of mice in each treatment group was limited to only four in this work. The results, however, were consistent and extended to four distinct lines of human mesothelioma, and the standard errors were small as shown in tumor growth curves. In view of the great need of effective therapies for mesothelioma, it appears that the combination of cisplatin and paclitaxel deserves a clinical trial based on the observations reported in the current investigation.

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