

Chemotherapy of Childhood Rhabdomyosarcomas Growing as Xenografts in Immune-deprived Mice¹

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ABSTRACT

Xenografts derived from the neoplastic tissues of children with rhabdomyosarcoma have been used in immune-deprived mice to examine the efficacy of agents known to be active against this disease, and in others that received either limited or no clinical evaluation. Two models were derived; xenografts were established from tumors obtained from either (a) untreated patients or (b) from patients who had become refractory to conventional therapy. Model a identified as being effective each of these clinically used agents: vincristine, dactinomycin, cyclophosphamide, and doxorubicin; mitomycin C and 5-(3,3-dimethyl-1-triazeno)-2-methylimidazole-4-carboxamide also showed activity, as did busulfan in one tumor line. Tumors derived from refractory patients were significantly less responsive to all agents examined.

INTRODUCTION

RMS³ arises *de novo* in skeletal muscle and represents between 4 and 8% of all malignant diseases in children under 15 years of age (21, 35, 40). It is the most common soft-tissue sarcoma in children (7, 20, 27) and represents approximately 10% of the solid neoplasms presented at this institution (31). RMSs in general are moderately sensitive both to radiation therapy (4, 6, 25) and to several chemotherapeutic agents (8, 13, 19, 26, 30, 33, 36-38). Using combined modalities of surgery, chemotherapy, and radiation therapy, patients with early-stage disease may be cured (12). The prognosis for children with more advanced disease, however, is poor (12, 22). At this institution, of 72 patients treated with CYCLO, VCR, and DACT, with or without DOX, 87% developed at least partial responses (29), although the complete response rate for chemotherapy alone was approximately 20%. Relatively few chemotherapeutic agents have been evaluated fully in childhood RMS (12) although CYCLO (13, 26, 36), DACT (8, 38), VCR (19, 33), and DOX (30, 37) have each shown significant activity. The regrowth of tumor during therapy suggests that conventional treatment is unable to eradicate the tumor before development of resistance. This presents a major problem, inasmuch as cross-resistance between 3 of the 4 agents used in primary treatment has been well documented [VCR, DACT, DOX; (5, 14, 32, 39)].

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³ The abbreviations used are: RMS, rhabdomyosarcoma; CYCLO, cyclophosphamide; VCR, vincristine; DACT, dactinomycin; DOX, Doxorubicin; LD₅₀, dose lethal to 10% of animals; DTIC, 5-(3,3-dimethyl-1-triazeno)-2-methylimidazole-4-carboxamide; Mito-C, mitomycin C; cis-DDP, cis-diamminedichloroplatinum(II).

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Evaluation of new chemotherapeutic approaches in RMS is hindered by several factors: (a) treatment is modified according to stage and site of primary disease; (b) patient accrual for any protocol is slow and hence the numbers of patients receiving one therapy protocol is often small; and (c) conventional combined-modality therapy is effective and, in patients with localized disease, is curative.

In more advanced disease, combined-modality therapy using combinations of CYCLO, DACT, and VCR is effective, but not curative; even after an initial response, relapse on therapy occurs in a high proportion of patients. It is with these drug-resistant patients that new agents are evaluated in Phase II trials. It is apparent that derivatives of anthracyclines and *Vinca* alkaloids, for example, would be unlikely to show marked activity under these circumstances. Consequently, such agents may not be evaluated further in previously untreated RMS. A preclinical model in which we may evaluate the efficacy of new agents against previously untreated and drug-resistant RMS would therefore be of value. Accordingly, we attempted to establish an appropriate laboratory model of childhood RMS by growing human tumors as xenografts in immune-deprived mice (18). Xenografts of various human cancer types have been shown to retain many characteristics of the tumor of origin (2, 15, 28) including chemosensitivity associated with the human disease (1, 10, 11, 16), and in specific instances xenografts show responses similar to those determined in the particular tumor or origin (9, 34). This study presents the responses to chemotherapy of xenografts established from previously untreated patients and studied in immune-deprived mice and the responses of such xenografted tumors derived from extensively treated children.

MATERIALS AND METHODS

Immune Deprivation. Four-week-old female CBA/CaJ mice (The Jackson Laboratory, Bar Harbor, Maine), were thymectomized. Three weeks later, they received 850 rads whole-body irradiation (250 rads/min Varian 4-MeV linear accelerator) and were subsequently injected i.v. with 2.5×10^6 syngeneic bone marrow cells as described previously (15). Tumor was implanted 2 weeks after irradiation. Mice were housed in an air-conditioned room (26-28°) which was lighted for 12 hr daily. Cages, food, and litter were autoclaved, and mice were transferred to clean cages twice weekly. Under these conditions, immune-deprived mice have essentially a normal life span and will support progressive tumor growth for periods in excess of 1 year.

Tumor Lines. Human xenograft lines HxRh12, and HxRh18 were established from previously untreated patients. Lines RD, LL, CB, and HxRh10 were derived from patients that had received extensive chemotherapy as detailed in "Results." Lines with the prefix Hx were derived directly from patient specimens; other lines were initially grown in culture before being established as xenografts. Tumor line RD was obtained from the American Type Culture Collection and has been described previously (24). Each line, grown as a xenograft, maintained

histological and histochemical similarity to the RMS of origin; each line demonstrated either a human karyotype, human-specific lactate dehydrogenase isoenzymes, or both (15).

For transplantation, donor tumors were excised and cut into approximately 3-cu mm pieces. One tumor piece was implanted s.c. into each dorsal flank of recipient mice which resulted in the growth of 2 discrete tumors. All procedures were performed in a Class B biohazard cabinet. The frequency of implants that gave rise to progressive tumor growth varied between tumor lines and between experiments, although this exceeded 70% in the experiments reported.

Measurement of Response to Chemotherapy. The growth of tumors was assessed by measuring 2 perpendicular diameters at 7-day intervals using vernier calipers. Each tumor approximated a spherical shape; hence, volume was calculated by substitution into the formula $[(\pi/6)(d)^3]$, where d is the mean diameter (17). Mice were treated when tumors had achieved a mean diameter of 8 to 10 mm (0.3 to 0.5 g); subsequent tumor growth was measured at 7-day intervals, and the delay in growth of treated groups was assessed at a time when these tumors had achieved 4 times the volume at treatment (17). Each agent was administered once only at 3 dose levels (LD_{10} , $0.66 \times LD_{10}$, and $0.33 \times LD_{10}$) to groups of 5 to 7 tumor-bearing mice. The LD_{10} was determined from previous experience with immune-deprived mice in this laboratory. With all agents reported, drug toxicity was manifested by weight loss and diarrhea or ataxia. Deaths were observed at the highest dose level used, which appeared as a consequence of drug-induced toxicity. Tumors were used between the third and sixth passage in mice. Data for the highest drug dose are presented although responses were dose dependent in each instance.

Chemicals. Busulfan was obtained from the Drug Synthesis and Chemistry Branch, Division of Cancer Treatment, National Cancer Institute, NIH. All other agents were obtained from pharmaceutical sources and were prepared within 1 hr of administration in the appropriate solvent.

RESULTS

For any tumor model to be of value as a screen for effective agents, it is essential that growth should be progressive and that growth rates for tumors of the same line but in different hosts should be similar. Variation in growth rates of human tumor xenografts, in particular those derived from breast adenocarcinomas, has often rendered evaluation of drug efficacy difficult. Typical growth curves for xenografts growing in s.c. sites for tumors derived from either previously untreated or previously treated patients are shown in Charts 1 and 2, respectively. The time required for doubling of tumor volumes ranged from 7.2 ± 1.5 (S.D.) days in line HxRh18 to 15.8 ± 6.6 days in LL tumors. Although there was some variation in the growth rate of individual tumors of the same line within a given passage, each of the tumor lines studied was considered useful for chemotherapeutic studies.

The response to chemotherapy of xenografts derived from previously untreated tumors is summarized in Table 1. Data presented show tumor responses at the highest dose level used. In each instance where a marked antitumor effect was measured (e.g., Table 1, +++ rating), a dose-response relationship was observed. The agents shown clinically to be effective in RMS demonstrated marked activity in 2 of the 3 xenograft lines studied. VCR was most effective in HxRh12 tumors, causing complete regressions and some long-term (>3 months) disease-free mice (Chart 3). Growth curves for line HxRh18 treated with VCR, DACT, CYCLO, and DOX and compared to one group of untreated control tumors are shown

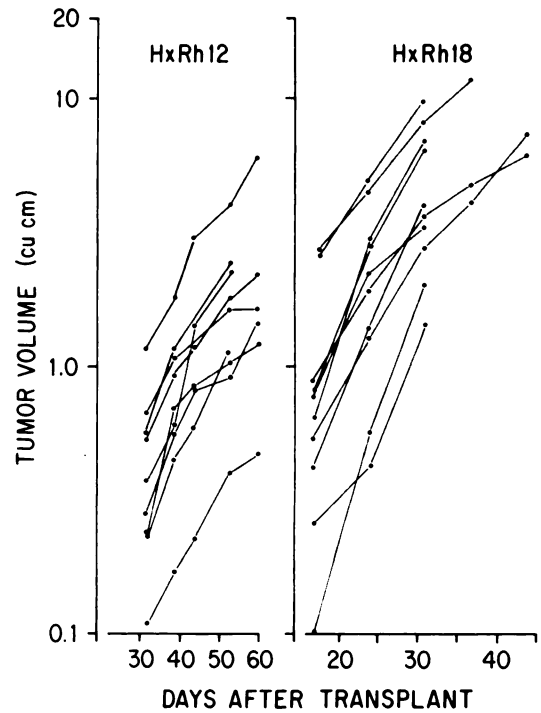


Chart 1. Growth curves for individual tumors growing s.c. in immune-deprived mice. Tumors were derived from previously untreated patient specimens. Tumors were transplanted bilaterally into 5 mice and were measured at 7-day intervals. Data show representative experiments.

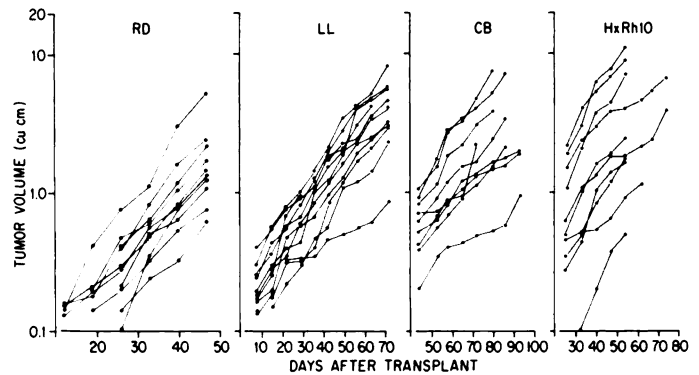


Chart 2. Growth curves for individual tumors derived from previously treated patients. Within a tumor line, rates of growth are similar in different mice. Tumors were transplanted bilaterally into 5 or 6 mice and were measured at 7-day intervals. Data show representative experiments.

Table 1
Chemotherapy of xenografts established from untreated tumors
Tumors were implanted s.c., and mice were treated with a single administration of agent when the tumors were approximately 8 mm in diameter. Data show responses at the LD_{10} level of dosage. Seven mice bearing bilateral tumors were used at each dose level.

Agent	Dose (mg/kg)	Tumor line HxRh12	HxRh18
VCR	3	++++ ^a	+++
CYCLO	150	+++	+++
DACT	0.3	-	+++
DOX	10	+++	+++
cis-DDP	7	++	++
DTIC	200	+	+++
Mito-C	3.25	-	++
Bleomycin	15	-	-
Busulfan	30	++	-

^a -, no growth inhibition; +, 1 to 1.5 volume doublings of growth inhibition; ++, 1.5 to 2 volume doublings of growth inhibition; +++, >2 volume doublings of growth inhibition; +++++, complete volume regressions, apparent "cures."

in Chart 4. Of the other agents examined, DTIC showed significant activity against HxRh18 and some activity in HxRh12. In addition, Mito-C, *cis*-DDP, and busulfan each showed activity in one tumor line while bleomycin was ineffective.

The sensitivity of xenografts derived from previously treated patients is summarized in Table 2. Details of patient therapy prior to establishing the xenograft line are also shown. In general, these tumors were considerably less sensitive to all agents tested. The RD line was moderately sensitive to VCR. Both busulfan and *cis*-DDP caused marked volume regression (>50%) in HxRh10 xenografts. However, in both instances, there were subsequent rapid regrowths, and little growth delay was measured in treated groups compared to control groups (Chart 5).

The response to chemotherapy of tumor line HxRh14 is of interest. The xenograft was derived from a tumor that recurred 2.5 years after discontinuation of therapy with VCR, CYCLO, and DACT after a complete response. Complete tumor regression also was attained in the xenografts after treatment with VCR (3 mg/kg), although all tumors subsequently regrew. Two other agents used in primary treatment, CYCLO and DACT,

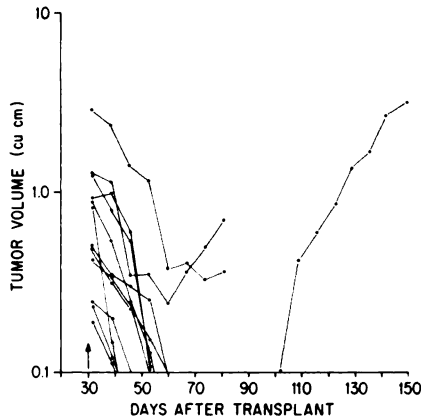


Chart 3. Growth curves for individual tumors of line HxRh12 treated with a single administration of VCR (arrow, 2 mg/kg). Treatment caused complete regression in 10 of 12 tumors and "cures" in 5 of 6 mice (1 death). Data were derived from 6 mice and show a representative experiment.

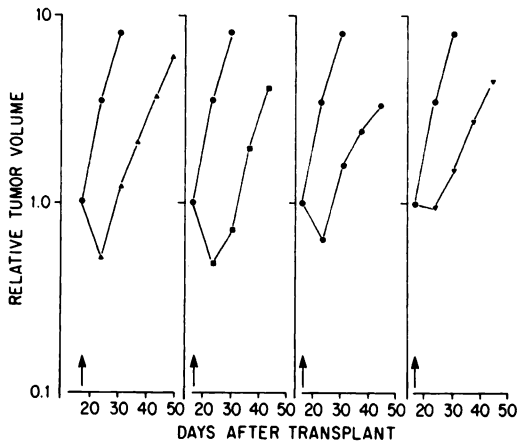


Chart 4. Response of HxRh18 tumors to maximally tolerated (LD₁₀) doses of VCR (▲), CYCLO (■), DACT (◎), or DOX (▼). ●, untreated. Each curve represents the mean growth for 14 tumors; tumor volume is expressed relative to volume at the time of treatment. The same control was used in each drug treatment group. For each point, S.E. < 10%.

Table 2
Chemotherapy of xenografts established from patients previously treated with the following agents^b

Agent	Dose (mg/kg) ^a	RD	LL	CB	HxRh10	HxRh14
VCR	3	++ ^c	+	±	+	++++
CYCLO	150	+	+	+	-	+
DACT	0.3	-	-	-	-	-
DOX	10	-	±	±	-	-
<i>cis</i> -DDP	7	-	-	±	±	+++
DTIC	200	-	-	-	±	+++
Mito-C	3.25	-	-	-	+	+++

^a LD₁₀ dose level.

^b RD, CYCLO, radiotherapy (refractory); LL, CYCLO, DOX (refractory); CB, VCR, CYCLO, DACT, DOX; radiotherapy, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, DTIC (refractory); HxRh10, VCR, CYCLO, DACT, DOX (refractory); HxRh14, VCR, CYCLO, DACT (complete response no evidence of disease 2.5 years, recurrence).

^c -, no growth inhibition; ±, either transient volume response or <1 volume-doubling inhibition; +, 1 to 1.5 volume doublings of growth inhibition; ++, 1.5 to 2 volume doublings of growth inhibition; +++, >2 volume doublings of growth inhibition; +++++, complete volume regressions.

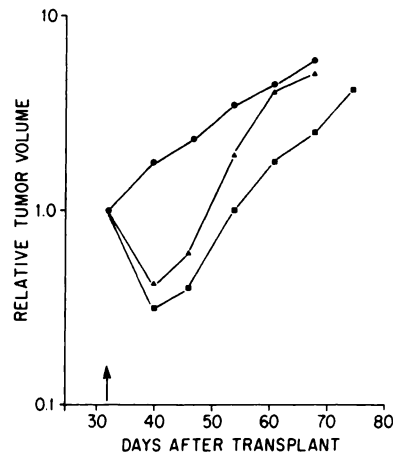


Chart 5. Response of HxRh10 tumors to busulfan (▲, 15 mg/kg; ■, 30 mg/kg; ●, untreated). Both dose levels induced significant volume reduction and rapid regrowth. Tumor volume is expressed relative to that at the time of treatment. Each curve represents the mean for 14 tumors. S.E. < 10%.

were far less effective while DOX did not retard the growth of HxRh14 tumors. Three other agents, *cis*-DDP, DTIC, and Mito-C, each showed marked activity against this tumor line.

DISCUSSION

Relatively few chemotherapeutic agents have received evaluation against previously untreated RMSs of childhood. Agents that have shown clinical activity (VCR, CYCLO, DOX, and DACT) comprise standard effective therapy, which in combination with other modalities is curative in patients with early-stage disease. New agents, therefore, are unlikely to be used in previously untreated patients and are evaluated in patients refractory to therapy. We have attempted, therefore, to develop laboratory models representative of untreated and drug-resistant RMS by growing tumor specimens as xenografts in immune-deprived mice. In this study, we have examined the tumor sensitivity to standard therapeutic agents used in the treatment of RMS and to other agents that have received either a limited evaluation or no evaluation in this disease. Our objective was to identify active compounds and not to optimize drug efficacy by varying the schedules of administration. Two tumor lines have been established from untreated patients. Lines HxRh12

and HxRh18 were sensitive to both VCR and CYCLO. In mice bearing HxRh12 tumors, VCR produced a high frequency of long-term, disease-free survival; DACT was inactive in line HxRh12 but moderately active in HxRh18 tumors, while DOX was active in both of these tumor lines. DTIC was marginally active in HxRh12 but showed good activity against advanced HxRh18 tumors [DTIC in combination has demonstrated activity in the treatment of RMS (3)]. Mito-C, *cis*-DDP, and busulfan were also active in at least one tumor line.

Against xenografts established from previously treated and refractory tumors, each of the agents examined was less effective. Line RD was moderately sensitive to VCR, although this was not surprising because the patient from whom the tumor was derived had not been treated with either an anthracycline or a *Vinca* alkaloid prior to establishing the tumor line in culture. Of the "non-standard" agents, Mito-C and busulfan were slightly effective in tumor line HxRh10. The response of HxRh14 is of interest. This line was established from a recurrent tumor in a patient who had been off therapy for 2.5 years with no evidence of disease after a complete response to treatment with a combination of VCR, DACT, and CYCLO. It is apparent that the xenograft is sensitive to VCR, but not to DACT or CYCLO. Both *cis*-DDP and Mito-C were active against this line.

One question that remains unanswered is the role of the host immune system in determining the magnitude of tumor response. After VCR administration, all HxRh14 tumors regressed below the level of detection, but all xenografts subsequently regrew which suggests relatively little interaction with the immune defense mechanism. However, in HxRh12 tumors treated with VCR, long-term disease-free survivors were observed. This may indicate that the host is capable of eradicating a tumor (or preventing regrowth) where only a relatively few tumor cells survive drug treatment. Thus, in this system, "cures" must be interpreted with caution. Whether these cured mice would accept a subsequent graft with HxRh12 cells may help to determine any changes in host immune status during the chemotherapy experiments. However, it has been shown in C57BL mice bearing syngeneic LSA lymphoma cells which are cured by treatment with 1,3-bis(2-chloroethyl)-1-nitrosourea that rechallenge with parental tumor cells is unsuccessful (23). This host resistance state was prevented by sublethal irradiation of the mouse before tumor implantation and thus may not operate in immune-deprived mice reported in our experiments where whole-body irradiation prior to tumor implantation had been administered.

At present, our model of previously untreated childhood RMS consists of 2 tumor lines. This model clearly needs to be expanded, but, even so, the procedure used appears to select for agents used in standard clinical protocols. In addition, Mito-C and DTIC have activity both in the model and in limited clinical evaluation (3, 12). The use of both models may help to select more rapidly new drugs with activity against previously untreated disease and agents that may prove valuable in children refractory to conventional therapy.

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