Coordinated Treatment of Childhood Rhabdomyosarcoma with Surgery, Radiotherapy, and Combination Chemotherapy

Charles B. Pratt, H. Omar Hustu, Irvin D. Fleming, and Donald Pinkel

SUMMARY

Twenty children with rhabdomyosarcoma were treated in a coordinated program utilizing surgery, radiotherapy, and combination chemotherapy. Therapy was determined by the stage of disease at which treatment was initiated. Of the 20 patients, 15 developed complete regression of tumor; 4 patients developed partial response. Of the 9 patients who are alive, 7 have been tumor free for 2 to 39 months. Concurrent radiotherapy and prolonged, intensive, combination chemotherapy are well tolerated following surgery for rhabdomyosarcoma. The coordinated use of these modalities offers prospects of curing more children who have this tumor.

INTRODUCTION

Results of treatment of childhood rhabdomyosarcoma with surgery or radiotherapy alone have been disappointing, with an overall survival rate of about 10% (1-4, 6, 7, 10, 16, 19, 26-28, 30). Pulmonary or bone metastases frequently ensue after complete resection of local tumor and lead to early death (7, 10, 21, 28). Chemotherapy with dactinomycin, vincristine, or cyclophosphamide, singly or in combination, results in tumor regression in many patients, only to be followed by rapid recurrence of tumor and resistance to that particular agent or agents (3, 5, 7, 8, 11-14, 19, 20, 23-25, 29-31).

The successful use of coordinated surgery, radiotherapy, and chemotherapy in treating rhabdomyosarcoma was first described in 1961 (21). Since then, we have demonstrated the superiority of utilizing a combination of all 3 drugs that are effective against this tumor, rather than using 1 of them alone (23, 24).

In 1968, a formal program was initiated for treating patients who have rhabdomyosarcoma. This program utilized staging of tumor and treatment with surgery, radiation therapy, and triple-drug combination chemotherapy. The objectives of this planned, coordinated program were to increase the frequency, extent, and duration of tumor regression, to prevent metastases, and to improve duration and quality of survival.

MATERIALS AND METHODS

Staging

Twenty patients with a confirmed tissue diagnosis of rhabdomyosarcoma who had received no previous chemotherapy were admitted to this study. Of the 20, 1 patient had received preamputation radiotherapy to the thigh. The tumors were staged in accordance with the following plan, reported previously (22, 23).

Stage I: Localized. Recognized tumor completely resectable.

Stage II: Regional. Adjacent structure, or local or regional lymph nodes involved; e.g., vagina + bladder, or vagina + pelvic lymph nodes: A, recognized tumor completely resectable; B, recognized tumor nonresectable or partly resectable.

Stage III: Generalized. A, distant metastases with normal bone marrow; B, distant metastases with bone marrow infiltration.

Of the 20 patients, 2 had localized, completely resectable tumor (Stage I). One of these 2 had been treated with irradiation to the thigh prior to amputation; postoperatively, a wound infection delayed initiation of chemotherapy for 2 months.

Three patients had regional, completely resectable tumor (Stage IIA); 9 patients had regional tumor that was partially or incompletely resectable (Stage IIB); 2 had generalized tumor without bone marrow involvement (Stage IIIA); and 4 had generalized tumor with bone marrow infiltration by rhabdomyosarcoma cells (Stage IIIB).

Age, Sex, and Tumor Site

Eight of the patients were females and 12 were males. The patients' ages ranged from 8 months to 20 years, 6 months with a median age of 8 years, 10 months. Six patients had primary tumors arising in the head or neck, including 3 in the orbit; 4 had primary tumors in the trunk, 6 in the genitourinary tract, and 4 in an extremity.

Histopathology

By our classification scheme (22), 15 patients had the compact or solid type of childhood rhabdomyosarcoma, 3 had the alveolar type and 2 had sarcoma botryoides.

Surgery

The exact surgical procedure used was determined by the location and extent of the tumor. For localized or regional
disease, radical surgical excision was carried out when possible. This encompassed the primary tumor with en bloc resection of all involved muscle, a generous margin of normal tissue, and the adjacent lymph node area, when feasible. For nonresectable regional or for generalized tumor, biopsies and careful exploration were used for determination of the extent of tumor and the structures involved; areas of tumor involvement were marked with metal clips for aid in radiation therapy. For nonresectable tumor, surgical reevaluation was performed at 12-week intervals. Repeat biopsies were performed as necessary for planning of further management.

Radiotherapy

Cobalt-60 teletherapy was delivered in a total tumor dose of 4000 to 6000 rads over a period of 5 to 8 weeks through ports extending well beyond the known confines of the tumor. Dose and port size were determined by the primary site and extent of tumor and the age of the patient. Radiotherapy was utilized for local tumors even when tumor was generalized. One patient also received radium treatment to the vagina following external cobalt-60 teletherapy.

Chemotherapy

Chemotherapy with vincristine (1.5 mg/sq m), cyclophosphamide (300 mg/sq m), and dactinomycin (0.4 mg/sq m) was administered i.v. at weekly intervals for 6 weeks, and then vincristine and cyclophosphamide were given every 2 weeks for 6 or 12 months. This program represents a variation from our previous schedule so as to provide more intensive chemotherapy early in the course of treatment (23, 24). The 6-week course of dactinomycin was repeated at 3-month intervals. Chemotherapy was initiated immediately after histological confirmation of diagnosis, concurrently with radiotherapy. Chemotherapy was administered for 6 months to patients with localized tumor and for 12 months to patients with regional or generalized tumor. Drug doses were adjusted to the biological tolerance of each patient by use of total white blood cell count as the primary guide.

Quantitation of Response

Response was determined quantitatively in relation to the clinical staging of disease with regard to frequency, extent, and duration. Except in those patients in whom the tumor was completely excised, complete response meant complete regression of all apparent tumor, including lesions noted by radiographic examination, and apparent clearing of tumor cells from the bone marrow. Partial response meant greater than 25% and less than 100% regression of apparent tumor masses measured as the products of 2 diameters and decrease in bone marrow infiltration by at least 50% on at least 2 consecutive aspirates. Failure to respond meant less than 25% objective decrease in apparent tumor or less than 50% decrease in bone marrow infiltration in at least 2 consecutive aspirates. Onset of response was dated from the time when at least 1 measurable lesion decreased by 25% or more. Duration of response was the interval between the date of response and recurrence, metastasis, or progression.

RESULTS

Therapeutic Effects

One patient with Stage I tumor was treated with triple-drug chemotherapy for 6 months after surgical excision. At 2 months following discontinuation of chemotherapy, pulmonary metastases appeared and chemotherapy with the same agents was reinstituted. After regression of the pulmonary metastases, the patient received radiotherapy to both lungs. Another patient with Stage I tumor is still receiving chemotherapy (Table 1).

Each of the 3 patients with Stage IIA tumor had complete responses which are continuing for more than 20, 27, and 39 months, respectively.

Of the 9 patients with Stage IIB tumor, 6 developed complete responses; the other 3 had partial responses. Of the 6 patients with complete responses, 3 remain in continuous complete remission for 1 to 23 months. One patient (No. 6) who remained free of tumor for 24 months developed generalized metastases, including bone marrow infiltration with rhabdomyosarcoma cells, 12 months after chemotherapy was discontinued.

One patient with Stage IIIA tumor developed a complete response and had no evidence of disease for 9 months; her response was considered partial because of failure of a contiguous bony lesion to heal. Another patient with IIA tumor (pulmonary metastasis) failed to respond.

All 4 patients with IIB tumor (generalized tumor with marrow infiltration) responded to initial chemotherapy with temporary clearing of tumor cells from the marrow. Of these 4 patients, 3 had extensive nodal, lung, bone, bone marrow, and cardiac metastases at autopsy.

Toxicity

Immediate toxicity in all patients included nausea and vomiting during the triple-drug chemotherapy. Generally, severity of these symptoms could be decreased with the use of antiemetic agents. Five patients complained of constipation and 3 developed oral ulcerations during intensive chemotherapy.

Delayed toxic effects of therapy included anorexia and weight loss of greater than 5% of pretreatment weight in 14 patients. Ten patients had alopecia. All patients developed depressed reflexes in the lower extremities and 9 patients developed absent patellar reflexes later in the chemotherapy period. One patient experienced jaw pain and another complained of paresthesias.

Six patients developed anemia, 4 patients developed leukopenia early during therapy, and 1 patient with Stage IIB tumor developed thrombocytopenia without bleeding. Persistent eosinophilia of greater than 10% was noted in 10 of the 20 patients. At the end of 1 year of chemotherapy, 1 patient had evidence of hemorrhagic cystitis. Radiation
Table 1  
*Childhood rhabdomyosarcoma: stage, treatment, and results*

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patient</th>
<th>Primary site</th>
<th>Extension</th>
<th>Surgery</th>
<th>Radiotherapy</th>
<th>Chemotherapy</th>
<th>Response</th>
<th>Duration of response (mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 Thigh</td>
<td>None</td>
<td>Hip disarticulation</td>
<td>Thigh, 2500 R (preamputation)</td>
<td>VCR-Cyclo-Dact&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Complete</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Paratesticular</td>
<td>None</td>
<td>Orchietomy, inguinal, iliac and paraaortic node dissection</td>
<td>None</td>
<td>VCR-Cyclo-Dact</td>
<td>Complete</td>
<td>2+</td>
<td></td>
</tr>
<tr>
<td>II A</td>
<td>3 Orbit</td>
<td>None</td>
<td>Enucleation, exenteration</td>
<td>Orbit, 4600 R</td>
<td>VCR-Cyclo-Dact</td>
<td>Complete</td>
<td>39+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 Orbit</td>
<td>None</td>
<td>Enucleation, exenteration</td>
<td>Orbit, 4460 R</td>
<td>VCR-Cyclo-Dact</td>
<td>Complete</td>
<td>20+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 Spermatic cord</td>
<td>Testis</td>
<td>Removal of mass, spermatic cord and testis</td>
<td>Pelvis, 4370 R; paraaortic nodes, 3600 R; paraaortic nodes, 3515 R</td>
<td>VCR-Cyclo-Dact</td>
<td>Complete</td>
<td>27+</td>
<td></td>
</tr>
<tr>
<td>II B</td>
<td>6 Prostate</td>
<td>Bladder</td>
<td>Needle biopsy of prostate</td>
<td>Perineum, 4150 R; Pelvis, 4450 R; abdomen, 2700 R</td>
<td>VCR-Cyclo-Dact</td>
<td>Complete</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Neck</td>
<td>Nodes vertebrae</td>
<td>Biopsy neck node</td>
<td>Neck, 6000 R</td>
<td>VCR-Cyclo-Dact</td>
<td>Partial</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Pelvis</td>
<td>Peritoneum</td>
<td>Partial resection of mass</td>
<td>Pelvis, 4450 R; abdomen, 2700 R</td>
<td>VCR-Cyclo-Dact</td>
<td>Complete</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Orbit</td>
<td>Maxillary sinus periorbitum</td>
<td>Enucleation, exenteration</td>
<td>Orbit, 5750 R</td>
<td>VCR-Cyclo-Dact</td>
<td>Complete</td>
<td>23+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 Orbit</td>
<td>Orbit</td>
<td>Biopsy</td>
<td>Face, orbit, 6000 R</td>
<td>VCR-Cyclo-Dact</td>
<td>Partial</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11 Gluteus maximus</td>
<td>Ischium, rectal shelf</td>
<td>Biopsy</td>
<td>Perineum, 4600 R; paraaortic nodes, 3580 R; pelvis, 3200 R</td>
<td>VCR-Cyclo-Dact</td>
<td>Complete</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Neck</td>
<td>Pleura, brachial plexus</td>
<td>Biopsy</td>
<td>Supraventricular area, 4350 R; mediastinum, 3870 R; axilla, 3650 R</td>
<td>VCR-Cyclo-Dact</td>
<td>Partial</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Uterus</td>
<td>Vagina</td>
<td>Hysterectomy</td>
<td>Lower medial pelvis, 4800 R; whole pelvis, 3350 R; paraaortic nodes 3200 R; local radium at vaginal surface, 8400 R</td>
<td>VCR-Cyclo-Dact</td>
<td>Complete</td>
<td>9+</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Vagina</td>
<td>Bladder, rectum</td>
<td>Complete hysterectomy</td>
<td>Lower medial pelvis, 4500 R</td>
<td>VCR-Cyclo-Dact</td>
<td>Complete</td>
<td>2+</td>
<td></td>
</tr>
<tr>
<td>III A</td>
<td>15 Retroperitoneum</td>
<td>Kidney, thoracic paraspinal muscle</td>
<td>Biopsy</td>
<td>Abdomen, 3420 R</td>
<td>VCR-Cyclo-Dact</td>
<td>Partial</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>III B</td>
<td>16 Thighs</td>
<td>Gluteus maximus lungs</td>
<td>Hip disarticulation</td>
<td>None</td>
<td>VCR-Cyclo-Dact</td>
<td>None</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17 Gluteus maximus</td>
<td>Perineum</td>
<td>Nodes, bone marrow</td>
<td>Pelvis, 3200 R; perineum, 2500 R</td>
<td>VCR-Cyclo-Dact</td>
<td>Complete</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Nodes, bone marrow</td>
<td>Biopsy</td>
<td>Hand, forearm, 4960 R; axilla, 3560 R</td>
<td>VCR-Cyclo-Dact</td>
<td>Complete</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Interossseous muscles of hand</td>
<td>Nodes, bone marrow</td>
<td>Biopsy</td>
<td>Hand and axilla, 4500 R</td>
<td>VCR-Cyclo-Dact</td>
<td>Complete</td>
<td>3+</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Interossseous muscles of hand</td>
<td>Nodes, bone marrow</td>
<td>Biopsy</td>
<td>None</td>
<td>VCR-Cyclo-Dact</td>
<td>Complete</td>
<td>3+</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> VCR-Cyclo-Dact, vincristine-cyclophosphamide-daunomycin.
dermatitis was not encountered in any of the patients in this study.

DISCUSSION

Treatment of rhabdomyosarcoma is generally unsatisfactory because of the sites of origin of these tumors and their tendency to infiltrate into local tissues. Few tumors can be completely removed. Distant metastases and recurrence near excision sites are frequent. At the time of surgery, it is often impossible to determine whether the tumor has extended beyond the margins of resection or whether seeding of lymph nodes, lungs, bones, or bone marrow by rhabdomyosarcoma cells has not already occurred.

Regression of childhood rhabdomyosarcoma usually occurs following supervoltage radiotherapy in doses of 3000 to 4000 rads, but doses of 5000 to 6000 rads over 6 to 10 weeks are required for complete tumor destruction (5, 17). Many tumors cannot be treated to this level because of their location and wide extension. Appropriate radiation ports are difficult to design because it is impossible to ascertain the distance of microscopic spread from apparent tumor.

The relationship of survival of patients with rhabdomyosarcoma to age at diagnosis, primary tumor site, and cell type has been discussed in detail by others (30). However, our experience indicates that the most important factor in prognosis is stage of disease at the time of initial therapy. In order to compare therapeutic results among institutions using different therapy programs, adoption of a uniform staging method will be necessary. Patients with Stage I rhabdomyosarcoma are considerably different from those with Stage III tumor. It is just as essential to classify tumor patients by stage in order to evaluate therapeutic results as it is to classify tuberculosis patients for this purpose.

Our early report (21) of successful treatment of childhood rhabdomyosarcoma by the combined use of surgery, radiation therapy, and chemotherapy has been confirmed by others (7, 11, 32). The value of simultaneous administration of actinomycin, vincristine, and cyclophosphamide to patients with this tumor, as described earlier (23, 24), has also been confirmed by a recent report (32).

Of 15 patients with previously untreated rhabdomyosarcoma admitted to this hospital in the 6-year period prior to the initiation of the present formal treatment program, 3 have survived. Each of the 3 survivors had Stage I or IIA tumor.

In the present program, coordinated therapy of rhabdomyosarcoma by surgery, radiotherapy, and triple-drug chemotherapy according to a formal protocol has resulted in prolonged, tumor-free survival of 7 of the 20 patients. Of these 7 patients, 3 (Nos. 3, 4, and 5) had Stage IIA tumor and are free of evidence of disease at 39+, 20+, and 27+ months, respectively. Three patients with Stage IIB disease (Nos. 9, 13, and 14) are free of evidence of disease at 23+, 9+, and 27+ months, respectively, and 1 patient with IIB disease is free of evidence of disease at 3+ months.

REFERENCE


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