Cyclophosphamide Dose Intensification during Induction Therapy for Intermediate-Risk Pediatric Rhabdomyosarcoma Is Feasible but Does Not Improve Outcome: A Report from the Soft Tissue Sarcoma Committee of the Children’s Oncology Group

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ABSTRACT

Purpose: More than half of pediatric rhabdomyosarcoma cases have intermediate-risk features and suboptimal outcome (3-year failure-free survival estimates, 55 to 76%). Dose intensification of known active agents may improve outcome.

Experimental Design: This pilot study evaluated the feasibility of dose intensification of cyclophosphamide in previously untreated patients ages < 21 years with intermediate-risk rhabdomyosarcoma. Induction therapy comprised four 3-week cycles of VAC: vincristine (V) 1.5 mg/m² on days 0, 7, and 14; actinomycin D (A) 1.35 mg/m² on day 0; and dose-intensified cyclophosphamide (C) on days 0, 1, and 2. The three cyclophosphamide dose levels tested were as follows: (a) 1.2 g/m²/dose; (b) 1.5 g/m²/dose; and (c) 1.8 g/m²/dose. Continuation therapy comprised nine additional cycles of VAC with 2.2 g/m²/cycle of C. Radiotherapy was administered at week 0 (parameningeal tumors with intracranial extension) or week 12 or 15 (all others).

Results: Between October 1996 and August 1999, 115 eligible patients were enrolled. Three of 15 patients treated at dose level 2 experienced life-threatening dose-limiting toxicity (typhlitis ± other severe toxicity). Dose level 1 was the maximum-tolerated dose, and 91 evaluable patients were treated at this level. The 3-year failure-free and overall survival estimates for patients treated at the maximum-tolerated dose were 52% (95% confidence interval, 41–64%) and 67% (95% confidence interval, 56–77%), respectively, at a median follow-up of 3 years.

Conclusions: A 64% increase in the standard cyclophosphamide dosage during induction (to 3.6 g/m²/cycle) was tolerated. However, outcomes were similar to those observed at lower dosages, suggesting that alkylator dose intensification does not benefit patients with intermediate-risk rhabdomyosarcoma.

INTRODUCTION

Rhabdomyosarcoma is the most common soft tissue sarcoma of childhood and accounts for nearly half of the soft tissue sarcomas diagnosed in children < 15 years of age in the United States (1). The past several decades have seen significant advances in the treatment of childhood rhabdomyosarcoma (2–4). However, by the mid-1990s, the probability of 3-year failure-free survival for patients in the most prevalent risk category (intermediate) remained between 55 and 76% (4). At that time, no novel chemotherapeutic agents were ready for phase III testing in this group of patients.

In 1996, the Intergroup Rhabdomyosarcoma Study Group (now the Soft Tissue Sarcoma Committee of the Children’s Oncology Group) opened a pilot study (D9502) to assess the feasibility of chemotherapy dose intensification in children with intermediate-risk rhabdomyosarcoma. Previous studies had established vincristine, actinomycin D, and cyclophosphamide (VAC) chemotherapy as the gold standard in the treatment of childhood rhabdomyosarcoma (2–4). Dose intensification of the vincristine or actinomycin D component was not contemplated because of neurotoxicity and hepatotoxicity, respectively. However, dose escalation of cyclophosphamide was undertaken on the basis of preclinical and clinical data, suggesting that this approach improves outcome.

Preclinical data indicate that cyclophosphamide has a steep dose-response curve (5, 6) and therefore that small increases in dose may substantially increase tumor cell kill. In rhabdomyosarcoma, bone marrow purging studies show a log-linear rela-
tionship between the dose of 4-hydroperoxycyclophosphamide (a congener of cyclophosphamide) and cell kill (7). Furthermore, preclinical studies in other tumor models suggest that resistance to cyclophosphamide can be overcome by dose intensification (8).

The most important acute side effect of cyclophosphamide is hematologic toxicity, which can lead to clinically relevant neutropenia and infection. However, this limitation may be ameliorated by the administration of exogenous hematopoietic cytokines, without imposing additional side effects (9). In previous studies of other chemotherapy regimens, cyclophosphamide doses > 4 g/m²/cycle were tolerable and did not delay subsequent treatment (10, 11).

Several lines of evidence suggest that dose intensification of chemotherapy can improve outcome in rhabdomyosarcoma. Patients with clinical group III rhabdomyosarcoma had a better outcome after treatment with the more dose-intensive repetitive pulse VAC on the Intergroup Rhabdomyosarcoma Study (IRS) II than after treatment with standard VAC on IRS-I (2, 3). Similarly, after the start of our clinical trial, Baker et al. (12) reported that certain subgroups of patients with embryonal rhabdomyosarcoma benefited from the greater alkylator dose intensity in IRS-IV compared with IRS-III. Studies in other pediatric and adult solid tumors also suggest that dose intensification strategies can improve outcomes (13–17).

This clinical trial was designed to evaluate the feasibility of intensifying the dose of the cyclophosphamide in the VAC chemotherapy regimen for children and adolescents with rhabdomyosarcoma. The main aim was to identify the maximum-tolerated dose (MTD) and toxicity profile of high-dose cyclophosphamide administered during the first four cycles of VAC chemotherapy in previously untreated pediatric patients with intermediate-risk rhabdomyosarcoma. A secondary objective was to determine the feasibility of giving high-dose cyclophosphamide-containing VAC concurrently with radiotherapy in patients with parameningeal primary tumors requiring radiotherapy at the outset of treatment. We also evaluated tumor response to induction therapy, event-free and overall survival, and the pattern of treatment failure to determine whether this therapeutic approach merits additional investigation.

PATIENTS AND METHODS

Patients. Patients were eligible for study entry on or after October 1, 1996, if they were <21 years of age and had intermediate-risk rhabdomyosarcoma, undifferentiated sarcoma (18), or ectomesenchymoma (19) that had not been treated with chemotherapy or radiotherapy. The following categories were defined as intermediate-risk disease (stage and clinical group designations have been defined previously; refs. 20, 21): embryonal histology, stage 2 or 3, clinical group III; embryonal histology, stage 4, clinical group IV, and age <10 years; alveolar histology, stage 1, clinical group II (node positive) or III (nonorbit/eyelid); alveolar histology, stage 2, clinical group II or III; and alveolar histology, stage 3, clinical group I, II, or III. A small subset of patients with high-risk disease were also eligible: those with a parameningeal primary tumor, stage 4, clinical group IV, of embryonal histology (if >10 years of age) or of alveolar histology. On July 1, 1998, the eligibility criteria were revised to include only patients with stage 2 or 3, clinical group III tumors or stage 4, clinical group IV parameningeal tumors and patients <10 years of age with stage 4, clinical group IV tumors of embryonal histology. Patients with primary rhabdomyosarcoma of the brain or spinal cord and those with multiple brain metastases or tumor cells in the cerebrospinal fluid were not eligible. Registration on the study was required within 72 hours of beginning treatment, and initiation of treatment was mandated within 42 days of the surgical procedure that established the diagnosis. Patients were required to have adequate organ function (grade 0 or 1 nephrotoxicity, total serum bilirubin ≤1.5× normal, serum aspartate aminotransferase and alanine aminotransferase activity <2.5× normal, no history of cardiac disease, and a shortening fraction >28% by echocardiogram or an ejection fraction >47% by radionuclide angiogram). The protocol was approved by the Institutional Review Board of each participating center, and written informed consent was obtained from all patients, parent(s), and/or guardian(s), as appropriate, according to institutional guidelines.

Treatment Plan. The treatment schema is shown in Table 1. Vincristine (1.5 mg/m²) was administered i.v. weekly or every 3 weeks for a total of 32 doses. Actinomycin D (1.35

<table>
<thead>
<tr>
<th>Table 1</th>
<th>D9502 protocol treatment schema</th>
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<tr>
<td><strong>Induction phase</strong></td>
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<td>Week</td>
<td>25</td>
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<tr>
<td></td>
<td>VAC</td>
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| Abbreviations: V, vincristine 1.5 mg/m²; A, actinomycin D 1.35 mg/m²; C, cyclophosphamide 2.2 g/m²; EVAL, clinical and radiographic evaluation; RT, radiotherapy.
* Cyclophosphamide dose at weeks 0, 3, 6, and 9 was higher, and determined by dose level assignment (see Table 2).
† Actinomycin D withheld at weeks 3 and 6 after radiotherapy at week 0, at weeks 15 and 18 after radiotherapy at week 12, or at weeks 18 and 22 after second-look surgery at week 12 followed by radiotherapy.
‡ Radiotherapy at week 0 for parameningeal primary tumors with intracranial extension and at week 12 for all others.
mg/m²) was given i.v. every 3 or 4 weeks for a total of 11 doses. Actinomycin D was withheld during radiotherapy (weeks 3 and 6 for those receiving radiotherapy at week 0, weeks 15 and 18 for those receiving radiotherapy at week 12, or weeks 18 and 22 for those undergoing second-look surgery at week 12 followed by radiotherapy). Cyclophosphamide was administered i.v. with vincristine ± actinomycin D every 3 to 4 weeks for a total of 13 doses. The study design called for dose intensification of cyclophosphamide during the first four cycles of induction chemotherapy (weeks 0, 3, 6, and 9). The cyclophosphamide dose escalation plan is described in detail below. During the remainder of treatment (weeks 12–37), a single dose of cyclophosphamide 2.2 g/m² was administered during each chemotherapy cycle (22).

Chemotherapy doses for children <3 years of age or whose body surface area was <0.6 m² were determined by dividing the dose (mg/m²) by 30 and multiplying by the child’s weight in kilograms. Mesna in doses equal to 20% of the cyclophosphamide dose was given before and 3, 6, and 9 hours after cyclophosphamide. Filgrastim (granulocyte colony-stimulating factor) given at a daily dose of 5 μg/kg by subcutaneous injection was started 24 h after the last dose of cyclophosphamide and continued until the absolute neutrophil count exceeded 10,000/μL. The next course of chemotherapy could not begin for at least 48 hours after the last dose of granulocyte colony-stimulating factor.

Patients who had parameningeal tumors with meningeal extension received radiotherapy to the primary tumor starting at week 0. All other patients underwent local control therapy (surgery, radiotherapy, or both) at week 12. If surgery was performed at week 12, the week 12 chemotherapy and radiotherapy (if needed) were deferred until week 15. If a gross total resection with negative microscopic margins was achieved, no radiotherapy was required. Patients with microscopic residual disease received 41.4 Gy in 23 fractions (1.8 Gy per fraction) to the tumor bed, and those with gross residual disease received 50.4 Gy in 28 fractions (1.8 Gy per fraction) to the tumor bed. A dose of 50.4 Gy was administered to all extramedullary sites of metastatic disease evident on imaging studies.

Cyclophosphamide Dose Escalation Plan. At the time that the protocol opened, the starting dose of cyclophosphamide was 1.8 g/m² on two consecutive days (3.6 g/m²/cycle). However, the protocol was amended after the enrollment of six patients at this dose level to prescribe 1.2 g/m² of cyclophosphamide on three consecutive days (also 3.6 g/m²/cycle) for future patients. This change allowed patients at all dose levels to receive chemotherapy over a 3-day period to facilitate comparison of toxicity. The six patients who received 1.8 g/m² cyclophosphamide on two consecutive days were excluded from all analyses of the toxicity and efficacy of dose level 1. Table 2 shows the planned dose levels of cyclophosphamide following protocol amendment. Thirty patients were to be treated at each dose level, and the dose was to be escalated only when toxicity data were available for all of these patients. Accrual at the same dose level continued during the review of toxicity. If eight patients in a cohort of 30 experienced dose-limiting toxicity (DLT) during the induction phase, the dose level would be considered too toxic. The MTD was defined as the dose level immediately below that at which unacceptable toxicity was identified. After the MTD was determined, an additional 20 patients were to be treated at the MTD to provide additional information about the toxicity profile. The study was later amended to increase patient accrual at the MTD to allow a better assessment of the toxicity of this regimen and the influence of dose intensification on outcome.

Definitions of Dose-Limiting Toxicity and Response. Toxicity was assessed at weeks 12, 24, and 40 and was graded according to the National Cancer Institute Common Toxicity Criteria, version 1.0. Dose-limiting nonhematologic effects were defined as any grade 3 and 4 toxic effects with the exception of grade 3 nausea and vomiting, fever, infection, mucositis that resolved within 7 days, hepatic toxicity that lasted to grade 1 within 14 days, and hematuria that resolved to grade 1 before the next course of chemotherapy. Moderate or severe veno-occlusive disease of the liver was also considered to be a DLT and was defined by clinical and/or imaging features of veno-occlusive disease, including any of the following features: total serum bilirubin concentration >6 mg/dL; noncardiogenic weight gain >5% of baseline; and ascites documented clinically or by imaging, renal deterioration, or hepatic encephalopathy. Grade 3 or 4 hematologic toxicity that was not reversed within 28 days of treatment was also deemed dose limiting, except in patients who had tumor involvement of the bone marrow.

Response to therapy was evaluated at weeks 12, 24, and 40. A magnetic resonance or computed tomography scan with contrast was performed to assess the primary tumor and a radio- and/or the appearance of new lesions. Progressive disease was defined as a ≥25% decrease in the sum of the products of the maximum perpendicular diameters of all measurable lesions, with no evidence of progression in any lesion and no new lesions. An objective response was defined as a 25 to 49% decrease in the sum of the products of the maximum perpendicular diameters of all measurable lesions, with no evidence of progression in any lesion and no new lesions. Stable disease was defined as a decrease <25% or an increase <25% in the sum of the products of the maximum perpendicular diameters of all measurable lesions and the absence of new lesions. Progressive disease was defined as a >25% increase in the sum of the products of the maximum perpendicular diameters of all measurable lesions and/or the appearance of new lesions.

### Statistical Considerations.

The duration of survival was defined as the time interval between on-study and death from any cause or most recent follow-up. The duration of failure-free survival was defined as the time interval between on-study and disease progression or death from any cause or last follow-up.
survival was defined as the time interval between on-study and progressive disease, second malignancy, death, or most recent follow-up. Survival and failure-free survival probability distributions were estimated by the method of Kaplan and Meier. Point estimates of survival and failure-free survival rates are presented, along with 95% confidence intervals calculated using Greenwood’s formula (23).

Cumulative incidence estimates were used to examine the pattern of treatment failure. Time to treatment failure was estimated as in failure-free survival. A failure was considered to be local if disease progression occurred only at the site of the primary tumor. A failure was defined as regional if the tumor appeared in regional lymph nodes, with or without a local failure. Any failure found elsewhere was considered to be distant, whether or not there was local or regional failure. The cumulative incidence rates were estimated by the methods of Kalbfleisch and Prentice (24).

RESULTS

Between October 1, 1996, and August 1, 1999, 125 patients were enrolled on the D9502 study. Ten patients were found to be ineligible for the following reasons: wrong diagnosis (n = 3); inappropriate stage/clinical group/histologic subtype (n = 6); and treatment initiated >42 days after the date of diagnosis (n = 1). Of the 115 eligible patients, 114 had intermediate-risk disease and 1 had high-risk disease.

**Cyclophosphamide Dose Escalation.** Of the 38 patients initially treated at dose level 1 (3.6 g/m² cyclophosphamide per cycle), only 1 experienced DLT (sudden death in the setting of fever and neutropenia after three cycles of chemotherapy). Therefore, enrollment of patients at dose level 2 (4.5 g/m² cyclophosphamide per cycle) was initiated. Among the first 15 patients treated at dose level 2, 3 experienced severe DLT. Typhlitis was observed in all three cases, although none had any known predisposition to gastrointestinal toxicity. In addition, one patient had pancreatitis, another developed an 8 × 10-cm area of perianal desquamation requiring i.v. hydration and narcotics, and a third experienced bacterial septic shock and diffuse alveolar damage. Besides the DLTs observed, the spectrum of side effects seen in the 15 patients treated at dose level 2 was similar to that observed in patients treated at dose level 1 (see Toxicity at the MTD section below). Grade 3/4 hematologic toxicity was universal; other grade 3/4 toxicities reported in >10% of patients included infection, nausea/vomiting, stomatitis, and motor neuropathy. Although the protocol specified dose de-escalation if 8 patients in a cohort of 30 experienced DLT, the life-threatening toxicity experienced by 3 patients among the first 15 patients enrolled at dose level 2 led us to conclude that this dose level was too toxic. Accrual at this dose level was halted, and patients were subsequently accrued at dose level 1 until a total of 94 eligible patients had been treated at this dose level. Among the 91 patients with available follow-up information, DLT was documented in only 3.

**Characteristics of Patients Treated at the MTD.** Table 3 summarizes the presenting features of the 91 patients treated at the MTD for whom follow-up information was available. The median age at the time of diagnosis was 4 years, and approximately two thirds of the patients were male. Parameningeal primary sites were most common, and favorable histologic subtypes (embryonal, botryoid, and spindle-cell) predominated. The majority of tumors were >5 cm in maximum diameter and were locally invasive. More than 80% of patients had localized rhabdomyosarcoma that was not grossly resected at the time of initial presentation. Fifteen patients (17%) had regional nodal involvement. Eight patients had metastatic disease involving the lung (n = 7), pleura (n = 3), bone (n = 2), soft tissues (n = 2), peritoneum/omentum (n = 2), mediastinum (n = 1), or bone marrow (n = 1).

**Toxicity at the MTD.** The grade 3 and 4 toxic effects that occurred in ≥10% of eligible patients enrolled at the MTD (dose level 1, 3.6 g/m² cyclophosphamide per cycle) are shown in Table 4. Hematologic toxicity was significant; all patients experienced grade 3 or 4 neutropenia, and approximately three quarters of patients experienced grade 3 or 4 anemia and thrombocytopenia. The proportion of patients with grade 3 or 4 hematologic toxicity was similar during induction and continu-
Table 4  Grade 3 and 4 toxic effects observed in ≥10% of 91 patients treated at the MTD during induction (weeks 0 to 12) or continuation (weeks 13 to 40) therapy

<table>
<thead>
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<th>Parameningeal tumor with intracranial extension (Radiotherapy at wk 0)</th>
<th>All others (Radiotherapy at wk 12 or 15)</th>
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|                      | Wk 0–12  
(n = 18)                  | Wk 13–40  
(n = 15)                  | Wk 0–12  
(n = 72)                  | Wk 13–40  
(n = 63)                  |
| Leukopenia          | 18 (100%)                  | 15 (100%)                  | 69 (96%)                  | 55 (87%)                  |
| Neutropenia         | 18 (100%)                  | 15 (100%)                  | 72 (100%)                  | 57 (90%)                  |
| Lymphopenia         | 13 (72%)                  | 10 (67%)                  | 48 (67%)                  | 32 (51%)                  |
| Anemia              | 13 (72%)                  | 11 (73%)                  | 64 (89%)                  | 49 (78%)                  |
| Thrombocytopenia    | 15 (83%)                  | 13 (87%)                  | 54 (75%)                  | 41 (65%)                  |
| Fever               | 3 (17%)                  | 1 (7%)                  | 9 (13%)                  | 6 (10%)                  |
| Infection           | 12 (67%)                  | 10 (67%)                  | 33 (46%)                  | 33 (52%)                  |
| Stomatitis          | 10 (56%)                  | 2 (13%)                  | 4 (6%)                  | 6 (10%)                  |
| Oral/Gastrointestinal mucositis | 7 (39%)                  | 5 (33%)                  | 8 (11%)                  | 8 (13%)                  |
| Nausea              | 4 (22%)                  | 1 (7%)                  | 6 (8%)                  | 5 (8%)                  |
| Liver dysfunction (aspartate aminotransferase, alanine aminotransferase) | 0 (0%)                  | 0 (0%)                  | 3 (4%)                  | 12 (19%)                  |
| Skin: acute         | 4 (22%)                  | 2 (13%)                  | 4 (6%)                  | 8 (13%)                  |
| Neurologic: sensory | 4 (22%)                  | 2 (13%)                  | 6 (8%)                  | 12 (19%)                  |
| Neurologic: motor   | 1 (6%)                  | 7 (47%)                  | 10 (14%)                  | 17 (27%)                  |

NOTE. One patient excluded due to missing toxicity data.

atination therapy. We did not observe significant cumulative hematopoietic toxicity after high-dose cyclophosphamide. The 40 weeks of protocol-mandated therapy was completed in a median of 45 weeks (range, 33 to 58 weeks).

The most common nonhematologic toxicity was infection, which occurred in 64% of patients and did not occur more frequently during induction than during continuation therapy. Sensory and motor neurotoxicity were seen more frequently in the continuation phase than in the induction phase, as expected from the chronic administration of vincristine. Other side effects were equally common during the two phases of therapy. Four patients died of toxicity. Three of these children died of infection during the continuation phase of therapy; in one case, the infection was associated with radiation pneumonitis and enteritis. The remaining child experienced sudden cardiac arrest of uncertain etiology during an otherwise uncomplicated hospitalization for fever and neutropenia after the third cycle of induction chemotherapy. An autopsy did not reveal a specific cause of death.

The 18 patients with parameningeal tumors that extended intracranially received radiotherapy during induction therapy; these patients experienced a degree of hematologic toxicity similar to that of patients with tumors at other sites. However, grade 3 or 4 stomatitis and oral/gastrointestinal mucosal toxicity was significantly more common in these patients than in those with other tumor sites (56 versus 18%), presumably because of the proximity of the gastrointestinal tract to the field of radiotherapy. Despite the higher incidence of mucosal toxicity in this subset of patients, there was no evidence that their radiotherapy was interrupted for significantly more days than that of patients who received radiotherapy concurrently with lower doses of cyclophosphamide. The median time between the start and end of radiotherapy was 41 days for patients with parameningeal tumors with intracranial extension and 40 days for other patients ($P = 0.13$).

Three secondary malignancies have been reported in patients treated on this study, yielding a 3-year estimated cumulative incidence of secondary malignancy of 2.4%. Two patients treated at dose level 1 developed myelodysplastic syndrome/acute myeloid leukemia associated with monosomy of chromosome 7, 1, 2, and 1.7 years after study enrollment; both patients died of the hematologic malignancy. One child treated at dose level 2 developed malignant fibrous histiocytoma of the chest wall 1.3 years after enrollment. This tumor was within the radiation field used to treat the rhabdomyosarcoma. Review of the pathology specimen obtained at the time of initial diagnosis confirmed the original diagnosis of rhabdomyosarcoma.

Response and Outcome in Patients Treated at the MTD.

Among the 91 patients who were treated at the MTD (3.6 g/m² cyclophosphamide per cycle during induction) and whose response data for week 12 after induction therapy were available, 22 (25%) experienced a complete response and 51 (59%) experienced a partial response. The complete response/partial response rate at week 12 for patients with parameningeal tumors (who had received concomitant radiotherapy) was similar to that of patients with tumors at other sites who had not received radiotherapy (76 versus 85%, $P = 0.46$). Among the 79 patients treated at the MTD for whom response data were available, 65 (83%) had experienced a complete response or partial response at the conclusion of all protocol-mandated therapy.

At a median follow-up of 3 years, the estimates of 3-year failure-free survival and survival were 52% (95% confidence interval, 41–64%) and 67% (95% confidence interval, 56–77%), respectively, for the 91 patients treated at the MTD for whom follow-up data were available (Fig. 1). Thirty-three of these patients experienced tumor recurrence or progression. There was an estimated 3-year cumulative incidence of 14% for local, 7% for regional, and 21% for distant recurrence.
In this pilot study, we found it feasible to increase the dose of cyclophosphamide by 64% during the first four cycles of induction chemotherapy (from 2.2 to 3.6 g/m²/cycle) for children and adolescents with intermediate-risk rhabdomyosarcoma. This dosage of cyclophosphamide was also tolerable in the subset of patients receiving concomitant radiotherapy for parameningeal tumors of the head and neck, despite a higher incidence of mucosal toxicity. Additional escalation of the cyclophosphamide dose to 4.5 g/m²/cycle during VAC induction therapy was associated with DLT that included typhlitis and other inflammatory or infectious complications. This finding was unexpected because similar doses have been used in combination with vincristine and doxorubicin without unacceptable toxicity (10, 25). However, it is possible that the use of actinomycin D in our regimen caused it to be more toxic than regimens that contain doxorubicin.

As expected, pancytopenia and infection were the predominant toxic effects of the dose-escalated cyclophosphamide regimen. However, the universal occurrence of grade 3 or 4 neutropenia was not significantly different from the experience in the IRS-IV study in which >90% of patients experienced myelosuppression after receiving 2.2 g/m²/cycle cyclophosphamide or 9 g/m²/cycle ifosfamide (26). Similarly, the 64% rate of severe infection was similar to the 55% incidence observed in IRS-IV. Myelodysplastic syndrome/acute myeloid leukemia associated with monosomy 7 was observed in two children treated at the MTD. Therapy-related myelodysplasia and acute myeloid leukemia are known complications of high-dose alkylator chemotherapy (27, 28). The 3-year estimated cumulative incidence of secondary malignancy in this study (2.4%) is similar to that observed in IRS-IV (2%) despite the use of higher cumulative doses of alkylating agents (26). Additional follow-up will be required to judge whether the incidence of late secondary malignancy is higher than that in previous rhabdomyosarcoma studies (29, 30).

It is noteworthy that there were no documented cardiac complications related to the use of high-dose cyclophosphamide in this study. However, one patient died suddenly of unexplained causes during an otherwise routine admission for fever and neutropenia after receiving three cycles of induction chemotherapy (3.6 mg/m² cyclophosphamide per cycle). We cannot exclude the possibility that cyclophosphamide-induced cardiotoxicity contributed to this sudden death, given previous reports of serious cardiac arrhythmia after the administration of high doses of cyclophosphamide (31–33).

Eighty-four percent of patients treated at the MTD were in complete response or partial response at week 12 after induction therapy. The week 12 response rate after standard VAC (2.2 g/m² cyclophosphamide) in IRS-IV was 73%.7 The slightly higher response rate in this study compared with IRS-IV was primarily due to a greater proportion of patients in partial response; the proportion of patients in complete response was 25% in this study and 23% in IRS-IV. At the completion of protocol-mandated therapy, 83% of the patients in this study were in complete response/partial response. This figure is similar to the 89% rate of response observed in a similar group of intermediate-risk patients on IRS-III (4).

Despite a favorable clinical response to this VAC regimen containing high-dose cyclophosphamide, the estimated rates of 3-year failure-free survival and survival for patients treated at the MTD were only 52% (95% confidence interval, 41–64%) and 67% (95% confidence interval, 56–77%), respectively. Direct comparison of these outcomes to those of patients treated on previous rhabdomyosarcoma studies is difficult, given slight differences in eligibility criteria. However, the estimated 3-year failure-free survival of 55 to 76% for children at intermediate risk on the IRS-IV study (26) suggests that this intensified cyclophosphamide regimen did not improve outcome. There also was no evidence that escalation of the cyclophosphamide dose during induction therapy led to improved systemic disease control. The 3-year cumulative incidence of distant recurrence was 8.8% in IRS-IV (26) and 8% in the current study. It is also noteworthy that the estimated rates of relapse-free survival and overall survival for patients treated at the MTD were 52% (95% confidence interval, 41–64%) and 67% (95% confidence interval, 56–77%), respectively.

7 J. Anderson, unpublished data.
was 21%. This figure is higher than the 7% estimated 3-year rate observed in the IRS-IV study (26), although that study included some patient subsets at lower risk of distant disease recurrence. The estimated 3-year cumulative incidence of local and regional recurrence (14 and 7%, respectively) was similar to the experience in IRS-IV.

At first glance, our results appear to contradict those of Baker et al. (12), who reported that alkylator dose intensification in the IRS-IV study improved the outcomes of patients with locoregional embryonal rhabdomyosarcoma as compared with the results of IRS-III. However, the improved outcomes in IRS-IV were restricted to two subgroups: patients with resected node-positive or un-resected tumors arising at favorable sites and patients with resected tumors at unfavorable sites. Patients in these subgroups were not eligible for enrollment in our study.

Given the steep dose-response curve of cyclophosphamide, it is unclear why substantial cyclophosphamide dose escalation failed to improve outcome in this study. There is no obvious pharmacokinetic or pharmacodynamic explanation. It is possible that the short duration (four cycles) of treatment with cyclophosphamide at the higher dose was insufficient to affect overall outcome, although this treatment led to a high rate of response. Previous studies in childhood rhabdomyosarcoma have demonstrated that the tumor response after induction therapy does not correlate with ultimate outcome (34, 35). Perhaps a more likely explanation for the failure of cyclophosphamide dose escalation to improve outcome is that some patients have a proportion of tumor cells that are extremely resistant to cyclophosphamide, even at significantly increased dose. Recent studies of high-dose therapy with hematopoietic stem cell rescue also suggest that additional dose escalation of alkylating agents does not significantly improve the outcome of rhabdomyosarcoma (36, 37).

In summary, significant dose escalation of cyclophosphamide during the 12 weeks of induction chemotherapy was feasible but did not discernibly improve the rates of response, failure-free survival, or survival or the cumulative incidence of distant disease recurrence. Our findings suggest that future clinical trials for patients with intermediate-risk rhabdomyosarcoma should focus on novel therapeutic approaches rather than on dose-intensification strategies.

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REFERENCES


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Cyclophosphamide Dose Intensification during Induction Therapy for Intermediate-Risk Pediatric Rhabdomyosarcoma Is Feasible but Does Not Improve Outcome: A Report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group
