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Original Paper

Treatment of Intermediate Risk Rhabdomyosarcoma and Undifferentiated Sarcoma with Alternating Cycles of Vincristine/Doxorubicin/Cyclophosphamide and Etoposide/Ifosfamide*

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Over 50% of patients with newly diagnosed rhabdomyosarcoma (RMS) are in the 'intermediate risk' group with a 3-year progression-free survival of approximately 65%. This group consists of stage 1, group III, non-orbit tumours; stage 2, group II and III; and all stage 3 patients utilising the Intergroup Rhabdomyosarcoma Study (IRS) staging system. The role of doxorubicin in the treatment of RMS has been controversial. Ifosfamide, both alone and in combination with etoposide, has significant activity in patients with RMS. The aim of this pilot study was to examine the efficacy and toxicity of a chemotherapy regimen of alternating cycles of vincristine/doxorubicin/cyclophosphamide and etoposide/ifosfamide for intermediate risk RMS. 30 patients with intermediate risk RMS or undifferentiated sarcoma (US) were treated with alternating cycles of vincristine/doxorubicin/cyclophosphamide (VDC) and etoposide/ifosfamide (EI) at planned intervals of 3 weeks. Local treatment of the tumour in most cases was performed after four cycles of chemotherapy, followed by an additional 10 cycles of chemotherapy. At a median follow-up of 37.5 months, the Kaplan–Meier estimate of 3-year event-free survival was 85% (95% confidence interval 72–99%). The overall survival at 3 years was 91% (95% confidence interval 80–100%). No patient died from toxicity. The most common toxicity was febrile neutropenia in 35% of VDC and 26% of El cycles. No nephrotoxicity or cardiac toxicity was seen. No patient progressed prior to week 12 local therapy. Alternating cycles of VDC and EI are an effective treatment for patients with intermediate risk RMS and US. Toxicity is tolerable. Delaying local treatment until week 12 does not compromise outcome. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

OVER THE past 21 years, the overall long-term event-free survival for patients with rhabdomyosarcoma (RMS) has improved significantly from 55% in the first Intergroup Rhabdomyosarcoma Study (IRS) to 72% in the third Intergroup Rhabdomyosarcoma Study [1, 2]. There have been many advances in the therapy of RMS, including changes in

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chemotherapy dose intensity, changes in radiation therapy doses, fields, and techniques; improvement in surgical approaches; and in the interdisciplinary management of these complex tumours.

Fifty-five per cent of patients with newly diagnosed RMS are in the 'intermediate risk' group with a 3-year progression-free survival of approximately 65% (Intergroup Rhabdomyosarcoma Study Group, data not shown). This intermediate risk group of patients consists of stage 1, group III non-orbit tumours; stage 2, group II and III; and all stage 3 patients, utilising the IRS staging and grouping systems (Tables 1 and 2). There is clearly much room for improvement in the cure rate in this subset of patients.

Vincristine, actinomycin-D, and cyclophosphamide (VAC) have been the traditionally used chemotherapeutic agents for the treatment of RMS [1–3]. The role of doxorubicin in the treatment of RMS has been controversial [2, 3]. Doxorubicin as a single agent in early studies resulted in response rates of 20–100% [4, 5] when given in relatively low doses and at low dose intensity. A dose intensive regimen of vincristine, doxorubicin and cyclophosphamide (VDC) has been demonstrated to have significant activity in extremely high risk sarcomas, both Ewing's and RMS. However, the population studied had a high percentage of patients with metastatic disease, so the overall survival was poor [6–8]. Ifosfamide, both alone and with etoposide, has documented activity in relapsed sarcomas, in particular RMS [9–13]. It is currently being compared in up-front therapy with cyclophosphamide in the fourth Intergroup Rhabdomyosarcoma Study. The recently completed Intergroup Ewing's Sarcoma Study demonstrated a significant improvement in overall survival in the patients receiving the treatment regimen utilising vincristine, doxorubicin, cyclophosphamide, etoposide and ifosfamide over the regimen without etoposide and ifosfamide [14].

Using the Intergroup Ewing's Study as a model and given the impressive phase II activity of etoposide/ifosfamide (EI) in RMS, the pilot protocol described here treated patients with intermediate risk RMS with therapy consisting of alternating cycles of VDC and EI. The goal of this protocol was to provide pilot data on the efficacy and toxicity of this regimen in a group of intermediate risk patients and to provide the basis for a phase III randomised trial evaluating this regimen.

PATIENTS AND METHODS

Patient eligibility

Eligible patients had newly diagnosed, previously untreated RMS or undifferentiated sarcoma (US). Patients were under 21 years of age, had normal renal, hepatic and cardiac function and provided written informed consent. Patients with local/regional lymph node involvement were eligible, but patients with distant metastasis were ineligible. Required evaluation for metastatic disease included computerised tomography of the chest, radionuclide bone scan and bilateral bone marrow aspirates and biopsies. Magnetic resonance or computerised tomography imaging of appropriate primary sites and involved nodal regions was also performed. For patients with parameningeal primaries, cerebrospinal fluid was analysed for the presence of tumour cells. Patients with embryonal tumours of the non-parameningeal head, orbit, and vagina and stage 1 paratesticular tumours were not eligible for this study. All other patients with non-metastatic RMS were eligible for this study. Patients with tumours of alveolar histology or USs of any site were also eligible. All tissue was reviewed centrally by one pathologist (AN) after study entry. Eight institutions from the upper midwest in the U.S.A. enrolled patients in this study.

The diagnosis of RMS was made in malignant, spindle, or round cell proliferations with confirmation by positive desmin and muscle specific actin staining; and negative stains for CD99 (MIC-2) and CD45 (leucocyte common antigen—LCA). In cases of negative or doubtful immunohistochemical results, the ultrastructural finding of Z-band structures, a marker of sarcomeric differentiation, was required as a diagnostic criterion.

Treatment plan

The chemotherapy schema is shown in Figure 1. Patients received vincristine, 1.5 mg/m^2 (maximum dose 2 mg); doxorubicin, 37.5 mg/m^2/day as an 18 h infusion daily for 2 days; and cyclophosphamide, 600 mg/m^2/day for 2 days with mesna, 360 mg/m^2/dose for five doses each day at weeks 0, 6, 12, 18, 24, and 30. The first 5 patients were given a dose of 60 mg/m^2/course of doxorubicin, then the dose was increased to 75 mg/m^2 per course for the remaining patients. Etoposide, 100 mg/m^2/day for 5 days with ifosfamide, 1800 mg/m^2/day for 5 days with mesna, 360 mg/m^2/dose for five doses were

Table 1. *Intergroup Rhabdomyosarcoma Study Group staging system*

Stage	Sites	Tumour (T)	Size	Regional nodes (N)	Metastasis (M)
1	Orbit Head and neck (excluding parameningeal) Genitourinary non-bladder/non-prostate	T_1 or T_2	a or b	N_0 or N_1 or N_X	M_0
2	Bladder/prostate Extremity Cranial parameningeal Other (includes trunk, retroperitoneum, etc.)	T_1 or T_2	a	N_0 or N_X	M_0
3	Bladder/prostate	T_1 or T_2	a	N_1	M_0
	Extremity		b	N_0 or N_1 or N_X	M_0
	Cranial parameningeal Other (includes trunk, retroperitoneum, etc.)				
4	All	T_1 or T_2	a or b	N_0 or N_1	M_1

T, confined to anatomic site of origin; a, ≤ 5 cm in diameter in size; b, > 5 cm in diameter in size. T_2, extension and/or fixation to surrounding tissue; a, ≤ 5 cm in diameter in size; b, > 5 cm in diameter in size. N_0, regional nodes not clinically involved; N_1, regional nodes clinically involved by neoplasm; N_X, clinical status of regional nodes unknown (especially sites that preclude lymph node evaluation). M_0, no distant metastasis; M_1, metastasis present.

Table 2. Clinical group stage system employed in Intergroup Rhabdomyosarcoma Studies I–III

Clinical group	Extent of disease and surgical result
I	(A) Localised tumour, confined to site of origin, completely resected
	(B) Localised tumour, infiltrating beyond site of origin, completely resected
II	(A) Localised tumour, gross total resection, but with microscopic residual disease
	(B) Locally 'extensive' tumour (spread to regional lymph nodes), completely resected
	(C) 'Extensive' tumour (spread to regional lymph nodes) gross total resection, but with microscopic residual disease
III	(A) Localised or locally extensive tumour, gross residual disease after biopsy only
	(B) Localised or locally extensive tumour, gross residual disease after 'major' resection ($\geq$ 50% debulking)
IV	Any size primary tumour, with or without regional lymph node involvement, with distant metastases, irrespective of surgical approach to primary tumour

administered at weeks 3, 9, 15, 21, 27, 33, 36, and 39. Vincristine was also given at weeks 1, 2, 7 and 8. Triple intrathecal chemotherapy with methotrexate, cytosine arabinoside and hydrocortisone was initially recommended for patients with parameningeal primaries and intracranial extension. This was subsequently revised to be administered only to patients with positive cerebrospinal fluid cytology along the current revised IRS guidelines. Only 2 of 14 patients received intrathecal chemotherapy early on for intracranial extension. The decision to use granulocyte-colony stimulating factor was left to the treating physician, but most patients received it. Echocardiograms to monitor cardiac function were performed at baseline and prior to weeks 12, 24 and 30. Follow-up echocardiograms were obtained at the end of therapy, 1 year after completion of therapy and then every 2–5 years, depending on the result.

After week 12 (following four cycles of chemotherapy), patients underwent therapy for local control of the tumour. The decision whether to utilise surgery or irradiation for local control was left to the treating physicians. Patients receiving irradiation as primary local therapy began treatment at week 12, as soon as possible after completing doxorubicin. In these cases the recommended dose was 5,040 cGy in 28 fractions to the tumour as visualised by three-dimensional imaging by computerised tomography or magnetic resonance imaging scans with margin in all directions (5 cm for extremity and 3 cm for truncal primaries). This was followed by a boost of an additional 540 cGy in three fractions to the tumour plus a 2 cm margin. If the patient underwent surgery, postoperative irradiation was specified for patients with gross or microscopic residual or if the surgical margin was 1 cm or less. Postoperative irradiation was begun at week 21. The treatment volume was to include the tumour bed plus a 3 cm margin for the initial 5,040 cGy in 28 fractions. In cases of residual disease, there was a boost of an additional 540 cGy in three fractions to the tumour bed with a 2 cm margin. Doxorubicin was not given during radiation therapy.

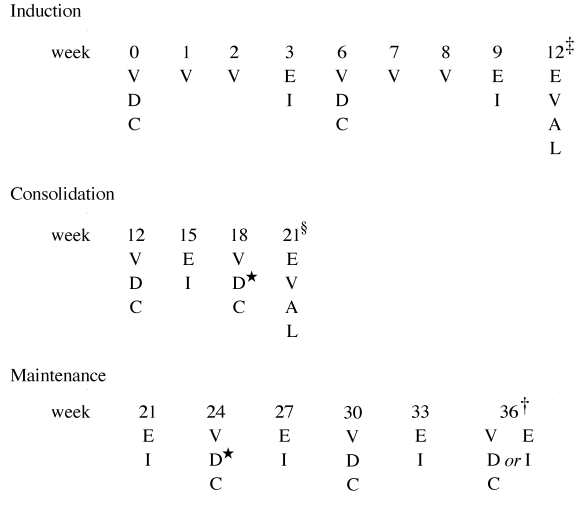

Figure 1. Schema for chemotherapy. V, vincristine 1.5 mg/m^2 (max 2 mg); D, doxorubicin 37.5 mg/m^2/day as 18 h infusion×2 days; C, cyclophosphamide 600 mg/m^2/day for 2 days with mesna 360 mg/m^2 for five doses; E, etoposide 100 mg/m^2/day for 5 days; I, ifosfamide 1800 mg/m^2/day for 5 days with mesna 360 mg/m^2 for five doses; Eval, evaluation. *Doxorubicin was omitted if radiation therapy (RT) was being given concomitantly. †VDC was given if D previously omitted at week 18 or 24, otherwise EI was given. ‡If primary RT was given, this occurred at week 12. Primary surgery also occurred at week 12. §If surgery followed primary RT, performed here. If RT followed surgery, RT began here.

Statistical methods

The overall and event-free survival curves were created using the Kaplan–Meier method [15]. Event-free survival was defined to be the time from study entry until death in remission, local or distant recurrence, development of second malignancy, or last contact.

RESULTS

Patient demographics

There were 34 patients entered into the study, of whom 30 were eligible. There were 3 ineligible patients. Reasons for ineligibility were distant nodal metastases in 1 patient and wrong diagnosis in 2 patients (primitive neuroectodermal tumour, extraosseous Ewing's sarcoma). 1 patient was lost to follow-up after being withdrawn from the study by his parents after the first treatment. Concordance with the institutional pathologist as to RMS subtype was seen in 28 of 30 cases. This report describes the 30 evaluable patients. 16 patients were $\leq$ 5 years of age, 4 were > 5–$\leq$ 10 years, and 10 were more than 10 years of age. The most frequent site of disease was parameningeal. Sites, stages, and histology are shown in Table 3. 1 patient with an alveolar parameningeal primary had documented regional lymph node involvement in the neck. No patient with a parameningeal tumour had positive cerebrospinal fluid cytology.

Survival and event-free survival

At a median follow-up of 37.5 months, the Kaplan–Meier estimate of 3-year event-free survival was 85% (95%

Table 3. Site, stage and histology distribution for all patients

Site	*n*	(Number) with stage/group	Histology
Parameningeal	14	(5) stage 3, group III	2 ARMS, 3 ERMS
		(8) stage 2, group III	1 ARMS, 7 ERMS
		(1) stage 3, group II	1 ERMS
Bladder/prostate	5	(1) stage 3, group III	1 ERMS
		(4) stage 2, group III	4 ERMS
Extremity	6	(3) stage 3, group III	2 ARMS, 1 US
		(2) stage 2, group II	1 ARMS, 1 US
		(1) stage 2, group III	1 ERMS at relapse ARMS
Head/neck	3	(2) stage 1, group III	2 ERMS (2 neck)
		(1) stage 1, group I	1 ARMS (1 lip)
Retroperitoneal	1	(1) stage 3, group (III)	1 ERMS
Trunk	1	(1) stage 2, group (I)	1 ERMS

ARMS, alveolar rhabdomyosarcoma; ERMS, embryonal rhabdomyosarcoma; US, undifferentiated sarcoma.

confidence interval 72–99%; Figure 2a). The overall 3-year survival was 91% (95% confidence interval 80–100%; Figure 2b). To date, 3 patients have progressed: 1 patient with a parameningeal primary tumour had a local recurrence in the radiation field; 1 patient with a parameningeal primary and 1 with an extremity primary had distant failures. 1 patient with distant failure has died. 1 patient developed acute myelogenous leukaemia (M4EO subtype with inversion of chromosome 16) 6 months following completion of chemotherapy and died of complications from leukaemia induction therapy. 14 patients have been followed for more than 36 months from diagnosis, 5 patients for 24–36 months, 10 patients for 12–24 months and 1 patient for less than 1 year.

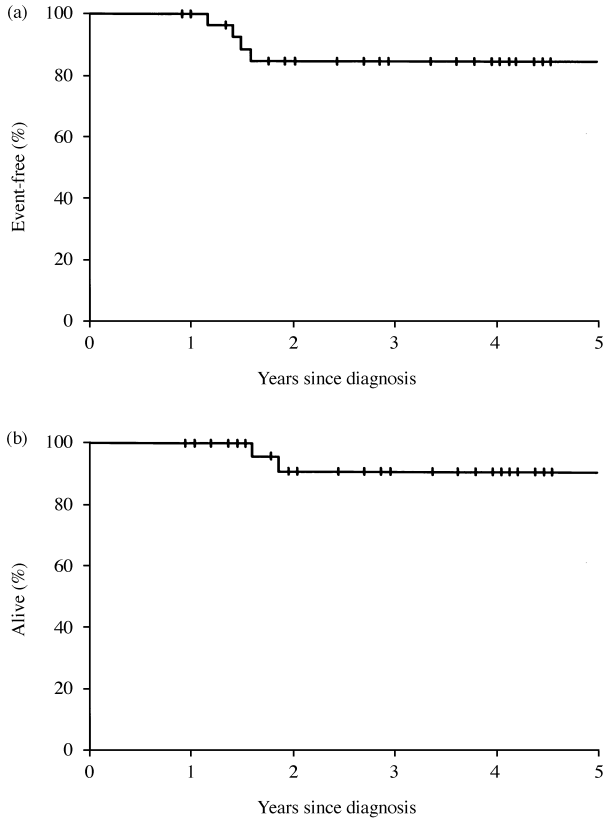

Figure 2. Kaplan–Meier (a) event-free and (b) overall survival curves.

Toxicity

Febrile neutropenia complicated 67 of 191 cycles (35%) of VDC, and 56 of 212 cycles (26%) of EI. Grade III or IV mucositis was seen following 32 of 191 cycles (17%) of VDC and 19 of 212 cycles (9%) of EI and was more common in patients with parameningeal primaries following radiation therapy. Haematuria occurred in 14 of 403 cycles of VDC or EI. Ten of these 14 cycles were in 2 patients with bladder/prostate primaries, the other four were in 3 patients with parameningeal primaries. No patient required a decrease in the dose of the oxazophosphorine due to cystitis. 1 patient developed a decreased cardiac ejection fraction from baseline resulting in the omission of doxorubicin for the last two courses. No patients are currently on cardiac medication.

Feasibility

One hundred and sixty-nine of 191 cycles (88%) of VDC and 196 of 212 cycles (92%) of EI were delivered at full dose. The reason for a decrease of doxorubicin was postradiation mucositis in 10 cycles (all during maintenance) and a decrease of cardiac ejection fraction from baseline (although still normal) in two cycles (1 patient). Doxorubicin and cyclophosphamide were both decreased in six cycles (all during maintenance) due to a delay in recovery of the neutrophil and platelet count. Vincristine was decreased due to foot drop in four cycles (1 patient). Etoposide and ifosfamide were decreased due to a delay in recovery of the neutrophil and platelet count following 13 maintenance cycles, due to mucositis in two maintenance cycles and error in one maintenance cycle. 2 patients did not receive the last three cycles of EI and 1 patient had the last course omitted due to prolonged cytopenias. The mean time for completion of induction chemotherapy (start of first treatment to start at week 12) was 97 days (range 82–144) in patients who did not have surgery prior to week 12 and 106 days (range 84–126) in those patients who did have surgery following completion of the first four cycles of chemotherapy (following recovery from week 9 chemotherapy). The scheduled time for completion of induction was 84 days. The mean time for consolidation therapy (beginning of week 12 chemotherapy to beginning of week 21 therapy) was 80 days (range 61–154), with a scheduled time of 63 days. The mean duration of maintenance was 168 days (range 90–215) with the scheduled time being 144 days. The patients who completed maintenance therapy early

($n = 3$) did so because the last three cycles were omitted due to prolonged cytopenias resulting in significant delays.

Local treatment

Bladder/prostate. 5 patients had bladder/prostate tumours. 3 underwent cystoprostatectomy and did not receive radiation therapy. 2 underwent both surgery and radiation therapy.

Parameningeal. There were 14 patients with parameningeal tumours. 11 had radiation alone, 2 had radiation plus surgery, and 1 had surgery alone.

Extremity. There were 6 patients with extremity tumours. 3 patients had surgery only, 1 had radiation only and 2 patients had both radiation and surgery.

Head/neck non-parameningeal. There were 3 patients with non-parameningeal head/neck primaries: two stage 1 group III embryonal neck tumours and one alveolar lip lesion. 2 patients had both surgery and radiation and 1 had radiation alone.

Other sites. There were 2 patients with other sites: retroperitoneal and trunk. Both of these patients had surgery and radiation therapy.

DISCUSSION

The group of patients described in this study had sites and stages which are considered to be intermediate risk with only 65% 3-year event-free survival with standard VAC therapy [1]. This pilot study evaluated an alternative treatment approach to improve outcome in this intermediate risk group. The combined modality treatment regimen resulted in an excellent event-free and overall survival in patients with non-metastatic intermediate risk RMS, 85 and 91%, respectively (Figure 2). 2 patients were not by definition 'intermediate risk': the patient with a trunk lesion who was stage 2, group I, and the patient with the lip lesion who was stage 1, group I. The reason for inclusion of the trunk lesion was that it was a below the clavicle primary with margins reported as negative but very close. The reason for inclusion of the patient with the lip lesion was that this patient had unfavorable histology which on IRS III was treated with a multiagent aggressive regimen. Tsokos and colleagues [16] and Newton and associates [17] have reported on poorer outcome of patients with alveolar histology.

The toxicity was quite tolerable. Contrary to other reports, there was no nephrotoxicity seen from ifosfamide. This may be because the cumulative dose was limited to 72 g/m^2 or that ifosfamide courses were given at 6 week instead of 3 week intervals, thus allowing the nephron to recover inbetween courses. Doxorubicin was given by infusion in this study and to date no cardiotoxicity has been observed. However, further follow-up of cardiac function is required to determine the long-term cardiac effects. 1 patient did develop a secondary leukaemia which has been described in association with topoisomerase inhibitors [18]. However, a recent review of a large study evaluating 519 patients with Ewing's sarcoma did not show an increased risk of development of secondary leukaemia or myelodysplastic syndrome in patients who were treated with vincristine, doxorubicin, actinomycin-D, cyclophosphamide, etoposide and ifosfamide ($n = 257$ patients) compared with those treated without etoposide and ifosfamide ($n = 262$) [19]. The cumulative alkylating agent and etoposide doses were the same as on the presently described regimen. However, longer follow-up and larger numbers of patients would be required to be able to draw conclusions about the leukaemogenicity of this regimen.

Delaying local therapy in the majority of patients until week 12 had no adverse effect on their outcome. No patient progressed during the 12 week period prior to local therapy. This is of particular note in patients with parameningeal primary tumours. 9 of these 14 patients had at least one high risk feature (intracranial extension, skull base erosion or cranial nerve palsy). In the patients with parameningeal primary sites, delay of radiation until week 12 allowed the administration of effective chemotherapy without compromising early dose intensity by the adverse interaction of chemotherapy with radiation. There was only one local failure among the 14 patients with parameningeal primary tumours, occurring within the radiation field 19 months from diagnosis. Caution should be used in comparing this very low rate of local recurrence in patients with parameningeal primaries to the IRS experience, because of limited numbers of patients in this study. However, the low local relapse rate in this high risk set of patients suggests further evaluation of the approach of delayed radiation in this group of patients.

RMS is an extremely complex tumour system. Although patients with embryonal tumors at orbital, paratesticular, and non-bladder prostate genitourinary primary sites are known to have excellent outcomes with disease-free survivals in excess of 90% with therapy limited to vincristine and actinomycin-D, patients with alveolar tumours and other non-metastatic tumours have had an intermediate outcome when treated on a VAC regimen.

The role of doxorubicin has been quite controversial and difficult to assess. In IRS III, patients with group II favourable histology tumours, excluding orbit, head, and paratesticular tumours, were randomised between vincristine/actinomycin-D and radiation therapy or vincristine/actinomycin-D and radiation therapy plus doxorubicin. There was suggestive statistical evidence that the addition of doxorubicin to the basic vincristine/actinomycin-D regimen improved clinical outcome in that study [2]. In IRS III, group I and II unfavourable histology tumours received pulsed VDC, VAC plus cisplatin, and radiation therapy and showed significant improvement in progression-free survival and survival rates for a comparable group treated less intensively in IRS II [2]. Group III patients with special pelvic tumours in IRS III fared better on the regimens with doxorubicin. However, the regimens were complex and also contained etoposide and cisplatin, making the contribution of doxorubicin to the improvement in survival from IRS-II difficult to ascertain.

Tremendous advances have been made over the past 20–25 years in curing RMS. Many effective treatment regimens have been described. However, the 'intermediate risk' group of patients still has only a 60–70% long-term disease-free survival rate on IRS III. We have described a treatment regimen with tolerable toxicity and excellent preliminary results for this group of patients. Further evaluation of this regimen in a randomised trial will allow assessment of its individual components.

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