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Granulocyte colony stimulating factor permits dose intensification by interval compression in the treatment of Ewing's sarcomas and soft tissue sarcomas in children

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Abstract

71 children with sarcomas were treated in a prospective pilot study to determine whether granulocyte colony stimulating factor (G-CSF) permits compression of the interval between chemotherapy cycles. Patients had Ewing's sarcoma/primitive neuroectodermal tumour (PNET), rhabdomyosarcoma, non-rhabdo soft tissue sarcomas or other advanced soft tissue tumours. The chemotherapy alternated vincristine–doxorubicin–cyclophosphamide and ifosfamide–etoposide, with G-CSF between courses. Therapy had two phases: induction (six cycles) and continuation (six cycles), which included primary tumour treatment with surgery and/or radiation. Chemotherapy cycles began every 14 days, or upon absolute neutrophil count (ANC) and platelet count recovery. The median chemotherapy cycle interval was 16 (11–48) days in the induction phase, with a median average relative dose intensification (ARDI) of 1.27 compared with every-21-day therapy. In the continuation phase, the median cycle interval was 21 days, with a median ARDI of 1.10. Radiation therapy prolonged chemotherapy intervals, whilst erythropoietin shortened them. Toxicity was modest for such chemotherapy. Event-free survival is comparable with or superior to that in recent large studies. G-CSF permits intensification of this regimen through interval compression. The impact of this approach on efficacy remains to be determined in a randomised trial.

Keywords: Ewing's sarcoma; Rhabdomyosarcoma; Antineoplastic agents combined; Child; Adolescent; Dose intensification; Drug administration schedule; Granulocyte colony stimulating factor; Leucocyte count; Platelet count

1. Introduction

There is much room for improvement in the treatment of Ewing's sarcoma and other paediatric sarcomas. The most effective arm of the recent intergroup Ewing's sarcoma study had a 3-year event-free survival of 69% for patients with localised tumours [1], and much lower survival for patients with metastases at diagnosis. Results for intermediate-risk and metastatic rhabdomyosarcomas are similar. (For the purposes of this paper, an intermediate-risk rhabdomyosarcoma is one which arises outside one of the favourable sites (orbit, superficial head and neck, vagina, paratestis) and is not metastatic at the time of diagnosis.)

Increasing the dose intensity (the quantity of a drug per unit of time) of chemotherapy is the subject of much current study as a means to improve the efficacy of treatment. For Ewing's sarcoma, there is evidence from retrospective analyses that the dose intensity of doxorubicin, in particular, influences prognosis [2]. In *in vitro* and animal models, the alkylating agents have a steep dose–response curve.

Granulocyte colony stimulating factor (G-CSF) has made the new generation of dose-intensive protocols possible by reducing the duration of neutropenia, the most dangerous toxicity of dose-intensive therapy. Virtually all such protocols explore the effectiveness of increasing the doses of chemotherapy, particularly the alkylating agents, while maintaining every-3-week treatment intervals. Some have held total doses of drugs constant by decreasing the number of cycles (for example, the experimental regimen on the most recent

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American intergroup Ewing's sarcoma study), whilst others have held the duration of therapy constant, thus increasing total doses.

An alternative approach to increasing dose intensity is decreasing the intervals between cycles whilst maintaining conventional doses. This has been referred to as 'interval compression', 'time intensification' or 'acceleration'. This approach has two potential advantages: it allows dose intensification of all agents, not just the alkylating agents; and it limits the time partially drug-resistant cells have to recover from one cycle of chemotherapy before they are assaulted by the next.

We conducted a prospective study of dose intensification through interval compression in 73 children and adolescents with Ewing's sarcoma, rhabdomyosarcoma and miscellaneous soft tissue sarcomas. We sought to determine the practical limit of interval compression using an alternating chemotherapy regimen of vincristine–doxorubicin–cyclophosphamide and ifosfamide–etoposide. We also sought to uncover any unusual toxicities associated with interval compression, and to estimate its efficacy in patients with Ewing's sarcoma.

2. Patients and methods

The study was initially opened for patients with newly diagnosed Ewing's sarcoma or peripheral primitive neuroectodermal tumour (PNET). It was later opened to patients with unresectable or metastatic rhabdomyosarcoma and other soft tissue sarcomas. Patients had to be 30 years of age or younger, and could have either localised or metastatic tumours. Those with pre-existing cardiac failure or renal insufficiency were ineligible, as were patients who had received previous chemotherapy or radiation therapy. The study was approved by the Institutional Review Boards at each of the participating institutions, and written informed consent was obtained from the parents or guardians of all patients, with consent or assent obtained from the patients themselves, as appropriate.

The treatment plan and chemotherapy doses are depicted in Fig. 1. Our intent was to give chemotherapy with the shortest possible interval between cycles, depending upon the recovery of neutrophils and platelets. Recombinant human granulocyte colony stimulating factor (filgrastim, Neupogen®, Amgen Inc., Thousand Oaks, CA, USA) was given subcutaneously at 5 mcg/kg/day, beginning 24 h after the end of chemotherapy, and was discontinued when the absolute neutrophil count (ANC) reached 1000/mm^3. The first 15 patients on the study had their blood counts checked every Monday, Wednesday and Friday and began their chemotherapy cycles as soon as the blood count criteria were satisfied. Subsequent patients had their blood counts checked on day 7 and day 14 of each cycle, and every Monday, Wednesday and Friday thereafter; their chemotherapy cycles began on day 14 or when count criteria were satisfied.

Blood counts were considered satisfactory when the ANC was at least 1000/mm^3 and the platelet count at least 75 000/mm^3. Chemotherapy cycles began at least 24 h after the last G-CSF dose. Full doses of all agents were delivered unless the interval between cycles was greater than 28 days, or toxicity attributable to a particular agent (such as vincristine neuropathy) occurred.

Primary tumour treatment consisted of surgical excision, irradiation or a combination. Patients with

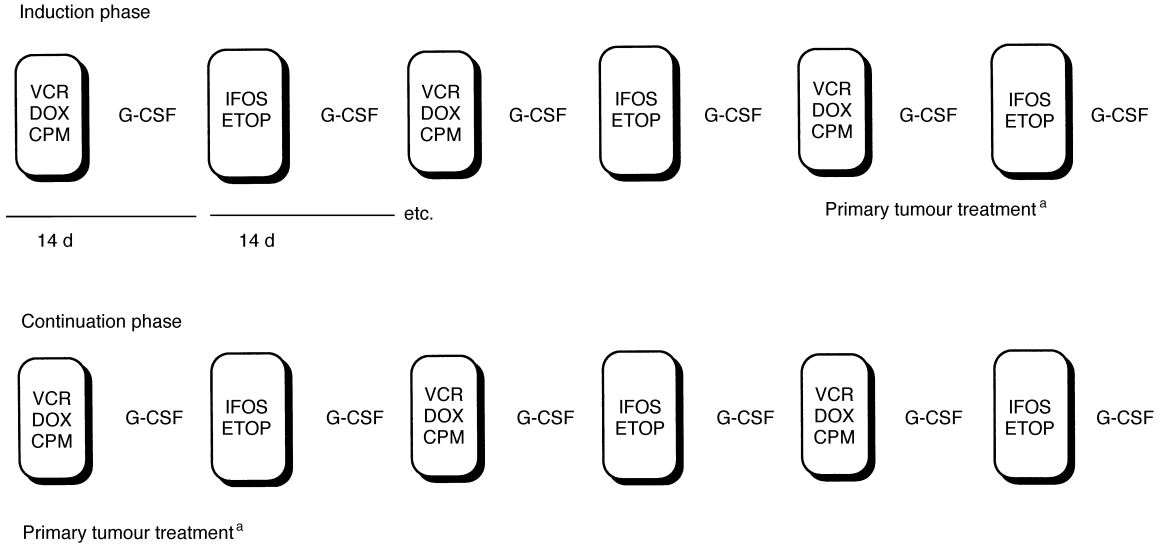

Fig. 1. Interval-compressed chemotherapy treatment plan. [a]If radiation, cycle order may be changed so that doxorubicin was not given during radiation. VCR, vincristine 1.5 mg/sqm (max. 2 mg); DOX, doxorubicin 75 mg/sqm as 72 h continuous infusion; CPM, cyclophosphamide 1200 mg/sqm; IFOS, ifosfamide 1800 mg/sqm/day for 5 days; ETOP, etoposide 100 mg/sqm/day for 5 days; G-CSF 5 mcg/kg/day SQ.

metastatic tumour at diagnosis had attempted excision or irradiation of all sites of gross disease. Gross unresectable tumour after induction chemotherapy received 5580 cGy megavoltage irradiation, with areas of microscopic residual disease after gross excision receiving 5040 cGy and the original tumour volume receiving 3600 cGy. Fields including more than 7 cm of the spinal cord were limited to 4500 cGy. All daily fractions were 180 cGy, and computed tomography-assisted treatment planning was employed.

3. Results

3.1. Patient characteristics

The characteristics of the enrolled patients are shown in Table 1. 73 patients were entered on the study, and 71 had enough data to be evaluable. 37 (52%) had Ewing's sarcoma or peripheral PNET; 19 (27%) had rhabdomyosarcoma, and the remaining 15 patients (21%) had a variety of soft tissue sarcomas and other soft tissue tumours. Of the 30 Ewing's sarcoma/PNET patients with localised tumours, 20 (67%) had tumours of the skull or trunk (vertebrae, clavicles, scapulae, ribs, pelvis). 9 of the 19 rhabdomyosarcoma patients (47%) had alveolar or pleiomorphic histology. The patients with miscellaneous sarcomas and other soft tissue tumours either had metastatic disease at diagnosis, or had locally aggressive tumours for which there was no established chemotherapy regimen.

3.2. Chemotherapy cycle lengths

We defined a chemotherapy cycle as lasting from the day chemotherapy began to the day it began again. Our experience with the first 15 patients showed that cycles less than 14 days long were clinically, administratively and socially difficult to achieve. Thereafter, we scheduled cycles to begin every 14 days, delaying them as necessary to satisfy blood count criteria and allow recovery from other toxicities.

Table 1
Patient characteristics

Sex			
Male	38		
Female	33		
Age			
Median (range)	11 (1–19) years		
Mean	10.4 years		
Diagnosis, site and stage		*n* (%)	Sub totals (%)
Ewing's sarcoma/peripheral PNET		37 (52)	
Localised			30 (81)
Skull or trunk			20 (67)
Proximal limb			4 (13)
Distal limb			6 (20)
Metastatic			7 (19)
Rhabdomyosarcoma		19 (27)	
Alveolar			8 (42)
Localised			7 (88)
Metastatic			1 (13)
Embryonal			7 (37)
Pleomorphic (localised)			1 (5)
Unclassified (localised)			3 (16)
Miscellaneous sarcomas		9 (13)	
Neurofibrosarcoma (metastatic)			2 (22)
Synovial sarcoma (metastatic)			2 (22)
Undifferentiated (metastatic)			2 (22)
Small cell osteosarcoma (localised)			1 (11)
Ectomesenchymoma (localised)			1 (11)
Mesenchymal chondrosarcoma (localised)			1 (11)
Other tumours		6 (8)	
Desmoplastic abdominal tumour			3 (50)
Anaplastic Wilms' tumour (metastatic)			1 (17)
Ovarian stromal tumour (regional)			1 (17)
Neuroblastoma			1 (17)

For all 667 evaluable treatment cycles, the median cycle length was 17 days (range: 11–48 days), and the mean 18.6 ± 5.6 days. The median cycle lengths grew longer as treatment proceeded (Fig. 2a). There was no difference in cycle duration between vincristine–doxorubicin–cyclophosphamide cycles and ifosfamide–etoposide cycles.

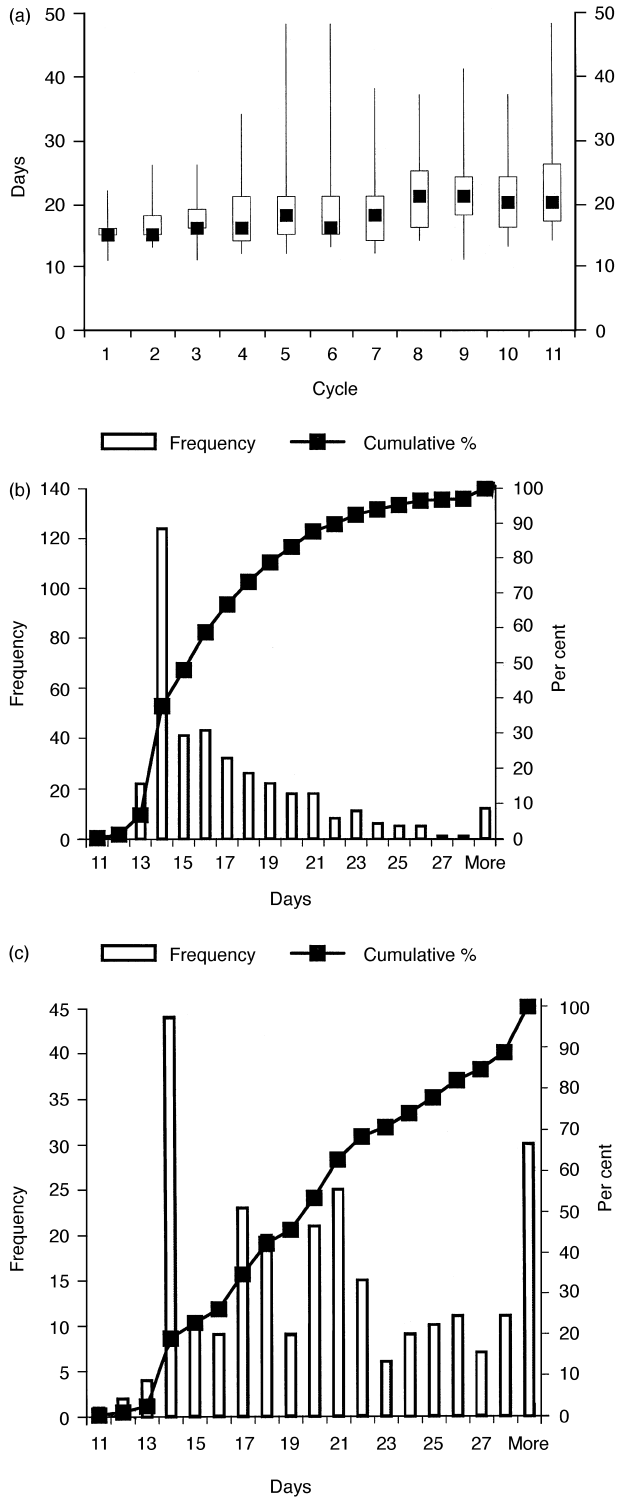

Fig. 2. (a) Chemotherapy cycle durations across treatment. The blocks indicate the median duration of each cycle, the boxes enclose the 25th and 75th percentiles, and the lines span the range of observed durations. (b) Induction phase cycle lengths, shown as a histogram (bars) and the cumulative proportion finished at each day (line). (c) Continuation phase cycle durations.

3.3. Chemotherapy cycle lengths in the induction phase

We defined the 'induction' phase of chemotherapy as the first six cycles of treatment (three with vincristine, doxorubicin and cyclophosphamide (VDC), and three with ifosfamide and etoposide (IE), and 400 cycles were evaluable. During this phase the median cycle length was 16 (11–48) days, and the mean 17.1 ± 4.7 days (Fig. 2b). The most common reason for delay was thrombocytopenia (75 cycles), followed by neutropenia with thrombocytopenia (22 cycles) and neutropenia alone (21 cycles) (Table 2).

3.4. Chemotherapy cycle lengths in the continuation phase

We analysed 267 cycles of 'continuation' chemotherapy, defined as the last six of the twelve total cycles (Fig. 2c). For all continuation cycles the median duration was 21 (11–14) days, mean 20.9 ± 6.3 days. The most common reason for delay was thrombocytopenia (121 cycles), with a combination of thrombocytopenia and another problem delaying 14 more cycles; only 10 cycles had neutropenia alone causing delay (Table 2).

3.5. Radiation therapy and chemotherapy cycle length

8 patients began their radiation therapy early in the induction period, usually because of cranial nerve palsies or spinal cord compression. This irradiation of marrow-bearing bones had a striking effect on chemotherapy cycle lengths (Fig. 3), with almost all of the delays from thrombocytopenia. The 35 induction cycles given during or after radiation therapy had a median

Table 2
Factors limiting interval compression[a]

Factor	Induction (400 cycles)	Continuation (267 cycles)
Platelets	75	121
Neutrophils	21	10
Neutrophils and platelets	22	8
Infection	15	10
Mucositis	8	2
Platelets and infection	3	6
Physician decision	7	9
Social and administrative	17	8

[a] Social and administrative delays were usually related to bed availability. Physician decisions were unspecified. Other causes for delay had four or fewer instances each, and included surgery (4 total), anal fissure (1), dermatitis in the radiation field (1), prolonged emesis (1), and other (13 total).

length of 19 (13–41) days, mean 21.9 ± 9.1 days, compared with a median of 15 days range and mean of 16.7 days S.D. for the cycles given without radiation therapy. In the continuation phase the effect of radiation therapy was similar, with median cycle lengths of 22 and 19 days in the irradiated and non-irradiated groups, respectively.

3.6. Erythropoietin and cycle duration

This study coincided with a randomised controlled crossover study of erythropoietin in children receiving chemotherapy for sarcomas [3]. 12 patients were enrolled in both studies, and they had 48 chemotherapy cycles with erythropoietin. We compared these 'EPO+' chemotherapy cycles with the 'EPO−' cycles from the same patients, combined with erythropoietin-free chemotherapy cycles from ten other contemporaneous Children's Hospital of Philadelphia patients.

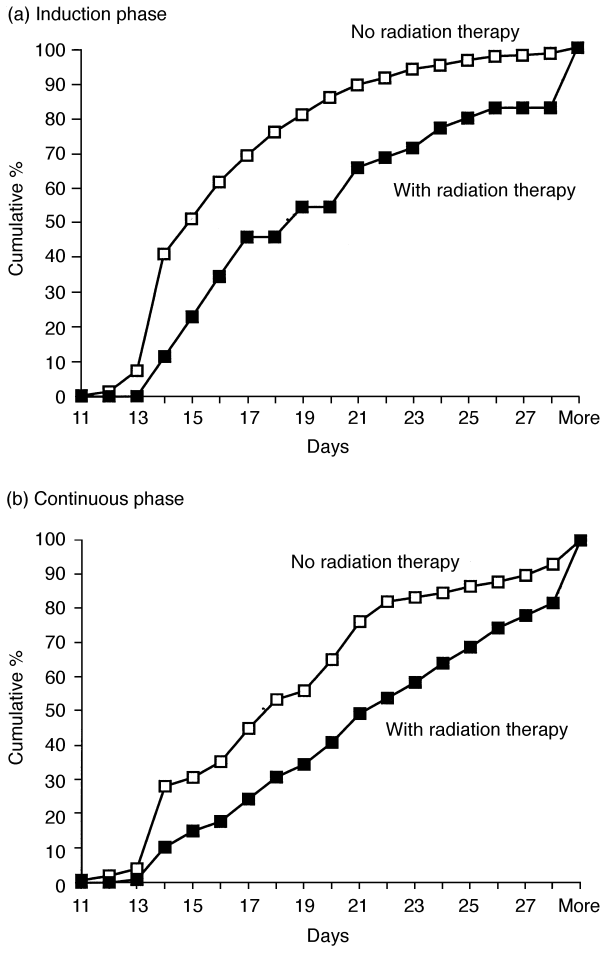

Fig. 3. Radiation therapy to marrow-bearing bones prolongs chemotherapy cycles in both (a) induction; and (b) continuation phases of chemotherapy. The curves show the cumulative fractions of chemotherapy cycles completed at each time.

We found no statistically significant EPO effect on chemotherapy cycle duration. However, cycles in which EPO was administered were significantly less likely to last longer than the median (16 days) than cycles without EPO in the continuation phase and overall ($P = 0.01$ and $P = 0.03$ by Fisher's Exact Test, respectively; Table 3). In the induction phase, the difference in the number of delayed cycles was not statistically significant. A reduction in the duration of thrombocytopenia appears to be the means by which EPO acts to aid interval compression.

3.7. Age and interval compression

We plotted the total duration of the induction phase as a function of age at study entry to determine whether age influenced interval compression. Regression analysis yielded a nearly-horizontal line, indicating that age did not influence our ability to reduce chemotherapy cycle duration (data not shown).

3.8. Toxicity

The toxicity of the compressed chemotherapy regimen was relatively modest (Table 4). Of 400 induction cycles evaluable for toxicity, febrile neutropenia occurred in 150 (38%), with 26 (7%) having a documented infection. Mucositis occurred in 76 cycles (19%), and nutritional support (either enteral or intravenous) was delivered during 95 cycles (24%). Only 15 cycles (4%) involved chemotherapy dose reductions for toxicity. In the continuation phase, among 267 evaluable cycles, febrile neutropenia occurred in 69 (26%), documented

Table 3
Effect of erythropoietin on interval compression[a]

	On time	Late	Total
All			
No EPO	24	81	105
EPO	18	31	49
Total	42	112	154
P value	0.03		
Induction			
No EPO	19	35	54
EPO	8	8	16
Total	27	43	70
P value	0.13		
Continuation			
No EPO	5	61	66
EPO	10	30	40
Total	15	91	106
P value	0.01		

[a] On time cycles lasted 16 days or less; Late cycles lasted longer than 16 days. EPO, erythropoietin. $P < 0.05$ considered significant.

Table 4
Toxicity[a]

Toxicity	Induction (400 cycles) *n* (%)	Continuation (263 cycles) *n* (%)	Total (667 cycles) *n* (%)
Neutropenic fever	150 (38)	69 (26)	219 (33)
Infection	26 (7)	31 (12)	57 (9)
Mucositis	76 (19)	34 (13)	110 (16)
Wt. loss/nutr. support	95 (24)	57 (21)	152 (23)
Doses reduced	15 (4)	38 (14)	53 (8)

[a] Weight loss is defined as a 10% or greater decline, while nutritional support includes enteral and parenteral supplementation. Uncommon toxicities included anal fissure (5 cycles total), prolonged emesis (4), otitis (2), oesophageal stricture (1), perirectal abcess (1), perianal cellulitis (1), proctitis (4).

infection in 31 (12%), mucositis in 34 (13%), and nutritional support in 57 (21%).

There was 1 toxic death, from an acute intra-abdominal catastrophe during a period of neutropenia. One patient with a thoracic spine peripheral PNET, who received irradiation involving the oesophagus, developed a severe oesophageal stricture and underwent a colonic interposition several months after the completion of therapy. 2 patients had doxorubicin discontinued after four doses, 1 because of an abnormal electrocardiogram and 1 because of a decrease in shortening fraction on echocardiography, but there was no case of clinical congestive heart failure. At least 3 patients had palmar-plantar erythema with desquamation, and several more sloughed their fingernails, but data on these side-effects were not systematically collected. There have been no cases of secondary myelodysplasia or leukaemia, and no reports of ifosfamide nephropathy or Fanconi syndrome. Overall, 4 patients experienced no recorded toxicity.

3.9. Dose intensification

We calculated the relative dose intensification (RDI) [4] compared with every-21-day chemotherapy in induction for the 57 patients who completed the induction phase and had complete data. An ideal patient receiving therapy every 14 days would complete induction in 84 days, and have an RDI of 1.5 [(6×21 = 126 days)/(6×14 = 84 days)]. The average relative dose intensification was 1.24, with a median of 1.27 (0.74–1.58), and a distribution heavily skewed towards higher dose intensification (Fig. 4). Radiation therapy to marrow-bearing bones had a distinct effect, with an ARDI of 1.31 for patients without radiation during induction and 1.08 for patients with radiation.

In the continuation phase, there were many delays related to primary tumour treatment, and 10 patients did not complete the continuation phase because of tumour progression. Thus, we evaluated the RDI for

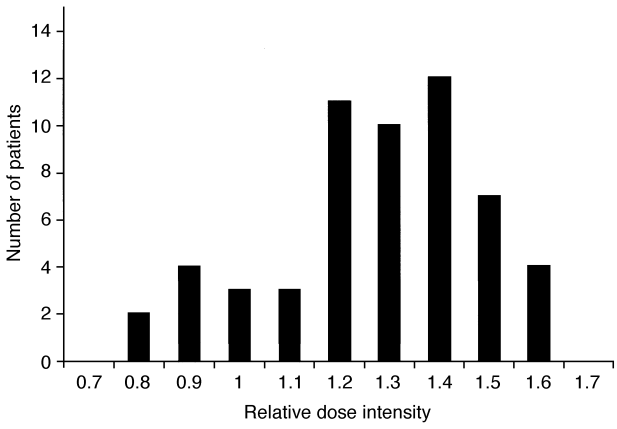

Fig. 4. Histogram of relative dose intensification achieved in the induction phase of therapy.

262 individual cycles, rather than for each patient through the entire phase. Overall, the ARDI was 1.10 compared with therapy every 21 days. Cycles without radiation had an ARDI of 1.17, whilst cycles during or after radiation had an ARDI of 1.00.

Dose reductions were uncommon: only 14 of 400 induction cycles (4%) were delivered at reduced doses; all of the reductions were 25%. In the continuation phase, 38 of 262 cycles (15%) had dose reductions, all of 25%.

3.10. Efficacy

Although the primary objectives of this small study did not include evaluation of the efficacy of interval-compressed chemotherapy, some analysis of event-free survival and overall survival is appropriate to ensure that the regimen is not markedly less effective. For the 30 patients with localised Ewing's sarcoma, the event-free survival is 73% and the overall survival is 85% at a median follow-up of 30 months (Fig. 5). One patient with a paraspinal PNET metastatic to breast and bone

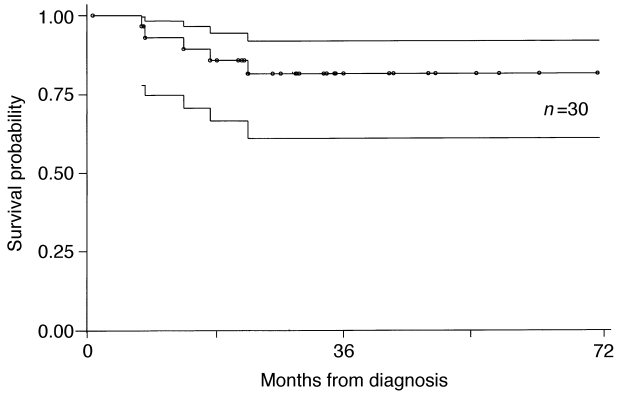

Fig. 5. Kaplan–Meier plot of event-free survival for 30 patients with localised Ewing's sarcoma and peripheral primitive neuroectodermal tumours. The outer lines enclose the 95% confidence intervals.

is alive and well 49 months from diagnosis, but 6 other patients with metastatic Ewing's/PNET and rhabdomyosarcoma have died of disease. Among 15 patients with intermediate-risk rhabdomyosarcoma, 12 are event-free and survive at a median of 36 months from diagnosis (range: 14–53 months).

9 patients had metastatic or unresectable miscellaneous sarcomas, including neurofibrosarcoma (malignant peripheral nerve sheath tumour), synovial sarcoma, and undifferentiated sarcoma. 3 of these patients had complete responses and 3 had partial responses to therapy; however, only 2 (1 with ectomesenchyoma, 1 with small cell osteosarcoma) remain alive. 3 further patients had desmoplastic small round cell tumours; only 1 (who had a complete excision) remains alive.

3.11. Patient and family acceptance

We did not formally survey patients and families for their reactions to the interval compression approach. However, no patient offered the study declined to participate, and many commented favourably upon its effect of shortening the disruptive period of chemotherapy by several weeks.

4. Discussion

Our data demonstrate that compression of the interval between chemotherapy cycles using G-CSF is a practical and well-tolerated method of increasing the dose intensity of chemotherapy. It has the advantage of intensifying the dose intensity of all of the agents in the combination. The dose intensity of the 1.27 ARDI achieved in the induction phase is equivalent to 3-week cycles of vincristine 2.54 mg/sqm, doxorubicin 95 mg, cyclophosphamide 1524 mg, ifosfamide 11.4 g and etoposide 635 mg. Although the dose intensity of the chemotherapy decreased from induction through continuation, the vast majority of cycles were delivered at full dose, and the overall dose intensity in continuation was still higher than every-21-day chemotherapy would have achieved. The toxicity of the regimen was relatively modest, and the number of dose reductions remarkably low.

We believe that G-CSF is an essential component of this approach. When used with intense chemotherapy, G-CSF results in a shorter, shallower period of neutropenia [5]. An attempt to compress chemotherapy intervals using GM-CSF in children with Ewing's sarcoma and related tumours at the National Cancer Institute was unsuccessful [6].

The population studied was relatively high-risk, with two-thirds (20/30) of the localised Ewing's sarcoma patients having tumours of the skull and trunk, against a usual proportion of half. Among the rhabdomyosarcoma patients, approximately half (9/19) had alveolar or pleiomorphic histology, about twice the usual rate. One of the few patients with localised rhabdomyosarcoma who progressed had an alveolar tumour of the hand with massive axillary adenopathy, a combination which has been shown to have the same prognosis as widespread metastases [7]. Another localised rhabdomyosarcoma patient who progressed was an infant with a massive pleiomorphic abdominal tumour. Despite the unfavourable population, this treatment produced excellent results in both groups of patients. Most of the patients with metastatic miscellaneous sarcomas had responses to a combination of chemotherapy and surgery, although most subsequently suffered tumour progression.

Thrombocytopenia was the factor most often responsible for delaying chemotherapy. This was particularly true when radiation therapy had been delivered to marrow-bearing bones. Erythropoietin appeared to reduce the delays from thrombocytopenia in this study. In a concurrent randomised placebo-controlled crossover trial of erythropoietin in patients undergoing chemotherapy for sarcomas at The Children's Hospital of Philadelphia, erythropoietin reduced platelet transfusions as well as red cell transfusions [3]. This is consistent with what we now know of the structural similarity of erythropoietin and thrombopoietin [8, 9]. Other clinical studies have failed to demonstrate erythropoietin stimulation of thrombopoiesis in a variety of settings, though the methods of analysis differed from ours [10–13]. The effects of erythropoietin, and other haematopoietic growth factors, may vary with the chemotherapeutic context, and the effect on platelet counts may be difficult to detect because of the wide variation in platelet counts between individuals and over time.

The relatively modest toxicity we observed is consistent with experience in adults with breast cancer using epirubicin, cyclophosphamide and G-CSF on a 14-day schedule, where only 9% of cycles required dose reductions [14]. The only unusual side-effects seen were sloughing of nails and rare palmar-plantar erythroderma. The former was painless, and the latter was also observed in a study of escalating doxorubicin every-14-day, with G-CSF between doses, in patients with advanced breast and ovarian cancer when the dose reached 125 mg/sqm [5]. Others have tried accelerating anthracycline-containing chemotherapy further: Piccart and colleagues tried reducing intervals from 22 to 10 days using epirubicin (120 mg/sqm), cyclophosphamide (830 mg/sqm) and G-CSF, but mucositis and skin toxicity prevented the use of intervals shorter than 13 days [15].

There is evidence that moderate increases in dose intensity can produce striking therapeutic gains. A randomised study of 105 patients with small cell lung cancer showed that relatively modest 30% increases in the initial doses of cisplatin and cyclophosphamide resulted in a marked improvement in the 2-year disease-free survival [16].

The timing of chemotherapy may also affect its efficacy, beyond changes in dose intensity. The recent Children's Cancer Group study of induction chemotherapy in acute myeloid leukaemia (CCG-2891) demonstrated that spacing the two initial cycles of chemotherapy 10 days apart gave markedly better results than the same chemotherapy given 14 days or more apart [17]. A randomised controlled trial of every-14-day chemotherapy for osteosarcoma is underway in the UK, and a few randomised studies of chemotherapy acceleration are planned or underway for breast cancer in adults as well.

This study demonstrates that delivering chemotherapy for Ewing's and soft tissue sarcomas more frequently than every 3 weeks is feasible. However, a randomised controlled trial will be necessary to determine whether interval compression can improve the efficacy of Ewing's sarcoma chemotherapy.

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