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Patterns of Chemotherapy-Induced Toxicities in Younger Children and Adolescents with Rhabdomyosarcoma: A Report from the Children's Oncology Group Soft Tissue Sarcoma Committee

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Abstract

Purpose—Patients aged older than 10 years with rhabdomyosarcoma (RMS) have an inferior outcome compared to patients aged 1–9 years which might be explained by toxicities (adverse events, AE) resulting in chemotherapy dose reductions.

Methods—AEs observed during one of 3 randomized chemotherapy regimens (VAC, VAI or VIE) in Intergroup Rhabdomyosarcoma Study (IRS)-IV were recorded. The incidence of toxicities by age and treatment regimen was determined. The odds of developing an AE in a particular age group (5–9, 10–14, and 15–20 years) were compared to the control age group, 1–4 years.

Results—657 patients were eligible for analysis. Estimated 5-year EFS were 78%, 83%, 67%, and 58% for age groups 1–4, 5–9, 10–14, and 15–20, respectively. Patients 15–20 years experienced less neutropenia (OR 0.43, $p < 0.0001$), thrombocytopenia (OR 0.41, $p < 0.0001$), anemia (OR 0.34, $p < 0.0001$) and infection (OR 0.41, $p < 0.0001$) compared to younger patients, despite receiving similar amounts of chemotherapy. In contrast, peripheral nervous system (PNS) toxicity was higher in adolescents older than 10 years (OR 4.18, $p < 0.0001$). Females experienced more neutropenia (OR 1.28, $p = 0.05$) and thrombocytopenia (OR 1.26, $p = 0.06$) compared to males.

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Conclusions—Adolescents receiving treatment for RMS experience significantly less hematologic and more PNS toxicity compared to younger children despite receiving similar amounts of chemotherapy. Although outcome is inferior in adolescents, it is unclear whether the differences in toxicity observed in our study impact on outcome. Future studies examining the age and gender-related differences in pharmacokinetics of chemotherapy are necessary.

Keywords

adolescent; rhabdomyosarcoma; toxicity; chemotherapy; age; gender

Introduction

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children and adolescents. The cure rates for patients with non-metastatic RMS have improved significantly from an estimated 25% in 1970 to 75% today.¹ This improvement in outcome is largely due to the systematic use of multimodal therapy including surgery, radiation therapy, and chemotherapy administered within the context of large cooperative group trials.^{1–4} In the setting of modern therapy, age at diagnosis is an important independent prognostic factor, with patients age older than 10 years faring worse when compared to patients between the ages of 1–10 years.^{5, 6} A recent analysis from the SEER registry confirms the poor outcome of adults (greater than 19 years of age) with non-pleomorphic RMS compared to children.⁷ Furthermore, adolescents and young adult patients with other cancers have also been known to have inferior clinical outcomes when compared to younger pediatric patients.^{8, 9} The reasons for these differences, although likely multifactorial, are not known. [reviewed in ¹⁰] One possible reason for the inferior outcome observed in adolescents with RMS may be a higher incidence of adverse events (AEs) resulting in dose modifications and consequently less total delivered therapy. To address this hypothesis, we evaluated the total chemotherapy delivered and AEs in patients with RMS 5–9, 10–14 and 15–20 years of age compared to younger children aged 1–4 years, treated on Intergroup Rhabdomyosarcoma Study (IRS)-IV.

Patients and Methods

We reviewed the toxicity data from 657 patients treated on IRS-IV; details of treatment and outcome have been published previously.⁴ Most patients with RMS or undifferentiated sarcoma and localized disease were randomly assigned to one of three chemotherapy regimens delivered over the initial 28 weeks: 1) vincristine, dactinomycin, and cyclophosphamide (VAC); 2) vincristine, dactinomycin, and ifosfamide (VAI); or 3) vincristine, ifosfamide, and etoposide (VIE). All patients received VAC for an additional 14 weeks. (Figure 1) The doses of cyclophosphamide and ifosfamide were 2.2 g/m² for 1 day per cycle and 1.8 g/m²/d for 5 days, respectively, both given with mesna. The dose of dactinomycin was 0.015 mg/kg/d x 5 days IV; maximum dose, 0.5 mg and vincristine 1.5 mg/m² IV; maximum dose, 2 mg. Patients with pre-existing renal abnormalities that predispose to potential nephrotoxicity (hydronephrosis, single kidney, or above-normal serum creatinine for age) were non-randomly assigned to VAC to avoid exposure to potential ifosfamide-induced nephrotoxicity and excluded from this analysis. For patients on

the VAI or VIE treatment regimens, the total dose of ifosfamide was limited to 72 g/m² to reduce renal toxicity. Patients received radiation therapy according to their IRS group, most often at week 9 of the protocol. The use of granulocyte colony stimulating factor (GCSF) was encouraged, but not mandatory, and was accordingly not systematically recorded. The total dose of chemotherapy delivered in mg was calculated as a percent of that prescribed by the protocol for each reporting period.

Statistical considerations

The rate of various AEs was modeled as a function of the age of the patient (4 categories: 1–4, 5–9, 10–14, 15–20), gender and treatment/reporting periods (3 treatments [VAC, VAI, VIE] and 4 reporting periods [protocol weeks 0–8, 9–19, 20–28 and 29–47] (12 categories) using generalized estimating equations, accounting appropriately for the correlation of the occurrence of specific AE in the same subject over the 4 reporting periods. The 4 age categories were chosen as the outcome is different between these 4 cohorts. From the modeling results, estimates of the OR of experiencing the AE in various age categories (compared to the baseline age group [age 1–4], by gender and in various reporting periods (compared to the baseline reporting period 1 [protocol weeks 0–8]) could be calculated. We were also able to assess differences in the risk of experiencing the AE in specific reporting period by treatment (VAC, VAI, VIE).

Event-free survival (EFS) was defined as the time from study entry to the first occurrence of progression, relapse after response or death from any cause. Patients not experiencing an event were censored at their last follow-up. EFS distributions were estimated using the Kaplan Meier survival analysis¹¹ and compared using the log-rank test.¹² The Cox proportional hazard model was used to assess the independent contributions of various factors to the risk of experiencing a protocol event.

Results

Patient Demographics

The demographics of patients included in this analysis are summarized in Table 1. The total dose of each chemotherapy agent (calculated as percent of total dose delivered in mg/dose intended) was similar across age groups, treatment regimens, specific agents and reporting periods. (Table 2) However, there were lower median doses of vincristine in the 4th reporting period for patients older than 10 years. Table 3 lists the absolute incidence of AE in each of the 4 reporting periods.

Adverse Event experience

Neutropenia—Lower rates of neutropenia were seen in reporting periods 2–3 for all patients, as compared to reporting period 1 (Table 3). In the first 3 reporting periods, less neutropenia was seen with regimens VAI and VIE compared to VAC for all age groups (Table 4). Patients aged 10–15 and 15–20 years had lower levels of neutropenia compared to other age groups (Table 5). Female patients experienced more neutropenia (OR 1.28, p=0.05) compared to male patients, and was independent of age category.

Thrombocytopenia—Statistically significantly higher rates of thrombocytopenia were seen in reporting periods 3 and 4 (Table 3) for all patients. Similar to neutropenia, lower rates of thrombocytopenia were seen with VAI and VIE in reporting periods 1–3 compared to VAC for all groups (Table 2). Patients aged 15–20 years had lower levels of thrombocytopenia compared to other age groups (Table 5). Female patients experienced more thrombocytopenia (OR 1.26, $p=0.06$) compared to male patients.

Anemia—Lower rates of anemia were seen in reporting periods 2–4, compared to reporting period 1 (Table 3). Significantly lower rates of anemia were seen for patients aged 10–14 and 15–20 years (Table 5). Somewhat more anemia was seen with VAI and VIE in reporting period 1 and somewhat more anemia seen for these patients in reporting period 4 when they received VAC (Table 2). There was no difference in the rate of anemia between male and female patients.

To summarize, less neutropenia and anemia was seen in reporting periods 2–4, whereas more thrombocytopenia was seen in these periods. Patients aged greater than 10 years and male patients experienced less hematologic toxicity generally.

Infection—Infection rates did not vary over reporting periods (Table 3). Patients aged 10–14 and 15–20 years had statistically significantly lower rates of infections (Table 5). Lower rates of infections were seen for VAI and VIE in reporting period 3 compared to VAC for all age groups (Table 2).

Peripheral nervous system (PNS) toxicity—Significantly more PNS toxicity was seen in reporting periods 2 and 3 (Table 3). Rates of PNS toxicity were higher in patients aged 5–9 years and much higher in those aged 10–14 and 15–20 years (Table 5). Significantly higher rates of PNS toxicity were seen for all patients randomized to VAI and VIE in reporting period 4 when they received VAC (Table 2).

Mucositis—Lower rates of mucositis were experienced in reporting periods 2–4 as compared to reporting period 1 (Table 3). Significantly higher rates of mucositis were experienced by older patients aged 5–9 and 10–14 years compared to children aged 1–4 years (Table 5). Treatment with VIE appeared to cause less muscositis than VAC and VAI in the first three reporting periods (Table 2).

Outcome

At a median follow-up of 7.7 years, the estimated EFS for all IRS-IV randomized patients was 75% (95% CI 72%, 78%). Factors predicting EFS in univariate analysis included age ($p<0.001$), stage ($p<0.001$), IRS Group ($p<0.001$), pathologic subtype ($p<0.001$) and primary site of disease ($p<0.001$). Since almost all patients received prescribed chemotherapy dose, this was not included in analysis of EFS. In multivariate analysis, age, stage, IRS Group and pathologic subtype remained statistically significantly associated with EFS. Estimated 5-year EFS by age was: age 1–4, 78%; age 5–9, 83%; age 10–14, 67%; age 15+, 58%. There was no difference in EFS by gender (data not shown).

Discussion

Adolescents with RMS have an inferior disease-related outcome and different patterns of chemotherapy-induced toxicity when compared to younger children. Adolescents older than 10 years of age experienced significantly less myelosuppression and more peripheral nervous system toxicity compared to children younger than 10 years of age. Age is a well known and robust prognostic factor in childhood RMS, with adolescents consistently faring worse than younger children, irrespective of histology and tumor site.^{5,6} We examined whether the tolerance to prescribed therapy, as measured by adverse events and percent of planned chemotherapy dose delivered, could explain the observed difference in outcome. Surprisingly, adolescents experienced significantly less hematotoxicity compared to younger children, despite comparable cumulative chemotherapy dose. Therefore, dose modifications in response to toxicity do not explain the age-related difference in outcome. Rather, the lower degree of hematological toxicity observed in adolescents could reflect relative lower systemic exposure to chemotherapy.

The dosing guidelines of anticancer therapy are often guided by a balance of efficacy and toxicity profiles; and for cytotoxic agents, the dose is often escalated until an acceptable level of myelosuppression is achieved. The degree of myelosuppression after chemotherapy has been demonstrated to correlate with outcome in certain diseases, and is possibly gender-specific. Analysis of the EURO-Ewing 99 protocol, which included 851 children and adults with Ewing sarcoma who received vincristine, ifosfamide, doxorubicin and etoposide (VIDE) chemotherapy, demonstrated that increasing age was associated with significantly less toxicity.¹³ The same study also reported that male gender was associated with less toxicity. In a recent exploratory analysis of the national Australian cancer registry, relapse-free survival of adolescents and young adults with cancer was found to be gender specific with males faring worse than females in those with Ewing sarcoma, osteosarcoma or Hodgkin lymphoma, which correlated with the degree of myelosuppression.¹⁴ Females with Ewing sarcoma achieved a lower nadir in neutrophil count compared to males after the first cycle of IVA/VAC chemotherapy (0.94 ± 0.64 versus 2.24 ± 1.08 , respectively). Similar gender-specific patterns were not seen in RMS or in children younger than 15 years.¹⁴ In a large retrospective analysis from the German Hodgkin Study Group, a higher prevalence of severe leukopenia (grade 3/4) during chemotherapy was correlated with better survival in female patients.¹⁵ Furthermore, the few male patients who also experienced severe leukopenia had a better outcome than their counterparts without severe leukopenia.¹⁵ In a cohort of women treated with cyclophosphamide, methotrexate and 5-fluorouracil for breast cancer, those who experienced at least one episode of grade 3/4 neutropenia had a better survival outcome compared to those who did not ($p=0.006$).¹⁶ Furthermore, myelosuppression remained significant ($p=0.05$) even when analyzed in a multivariate cox-proportional model with other known prognostic factors. In our analysis, female patients were more likely to experience neutropenia; however, gender did not influence EFS. It is conceivable that the minimal myelosuppression observed in adolescents in the IRS-IV study reflects a relative inadequacy of alkylating agent, possibly contributing to an inferior outcome in this age group.

Based on these observations, it is possible that escalating the dose of alkylating agent in adolescents with intermediate risk RMS would improve survival; however, data to date do not support this hypothesis. The dose of cyclophosphamide has increased significantly in successive IRS/COG trials from approximately 0.9 g/m²/course during IRS-III¹⁷ to 2.2 g/m²/course during IRS-IV in order to achieve equivalent hematologic toxicity with the ifosfamide-containing arms, VAI and VIE.⁴ The total cumulative dose of cyclophosphamide was 26.4 g/m² for those randomized to VAC alone. However, no improvement in FFS for either intermediate-risk embryonal RMS (3 year failure-free survival (FFS) on IRS-III, 74% versus IRS-IV, 75%, p=0.47) or intermediate-risk alveolar RMS (3 year FFS on IRS-III, 70% versus IRS-IV, 64%, p=0.35) was seen despite the escalation of cyclophosphamide cumulative dose and dose intensity.^{4, 18} The same cyclophosphamide dose per course (2.2 g/m²) was maintained during D9803.¹⁹ The total dose of cyclophosphamide on the VAC regimen of D9803 was 30.8 g/m² compared with 25.1 g/m² on the VAC/VTC regimen, giving the VAC/VTC regimen 20% less cyclophosphamide. Despite the lower total cyclophosphamide dose on the VAC/VTC regimen, the outcome of patients was similar to that on IRS-IV and on the VAC regimen of this study. Furthermore, cyclophosphamide dose escalation may be implicated in the severe hepatopathy observed in very young children during both IRS-IV and D9803.^{20, 21} In all of these studies, the impact of cyclophosphamide dose on FFS was not specifically analyzed by age older than 10 or 15 years.

Due to the aforementioned short term toxicity of alkylating agent, long-term gonadotoxicity, and the lack of improvement in FFS with higher doses, the current series of COG RMS studies use a dose of 1.2 g/m²/course cyclophosphamide for all patients. The experimental arm of the current COG intermediate risk RMS (ARST0531) replaces half of the VAC courses with vincristine and irinotecan cycles, resulting in a total cumulative dose of 8.4 g/m² of cyclophosphamide compared with 16.4 g/m² in the VAC arm. We will await the results of this study to determine whether the addition of irinotecan is sufficient to rescue adolescents from this reduced dose of cyclophosphamide.

The dose of alkylating agent has been escalated unsuccessfully in other sarcoma studies. For example, increasing cyclophosphamide dose intensification from 1.2 g/m²/dose daily x 3 days to 1.8 g/m²/dose (a 64% increase to 3.6 g/m²/cycle) in patients with intermediate risk RMS did not improve survival.²² However, out of 91 patients treated, only 20 (22%) were greater than age 10; outcome was not analyzed by age in this study. A German study examined replaced cyclophosphamide with ifosfamide and etoposide in standard chemotherapy for high risk localized RMS and found no improvement in survival; albeit in comparison to non-randomized historical controls.²³ A randomized study in localized Ewing's sarcoma also failed to show a benefit of escalating the dose-intensity of alkylating agent.²⁴

Cyclophosphamide is a prodrug undergoing a complicated process of metabolic activation and inactivation.²⁵ In a population of pediatric neuroblastoma patients, considerable inter-patient variability was observed in the pharmacokinetics of cyclophosphamide and two of its metabolites, hydroxycyclophosphamide and carboxyethylphosphoramide mustard.²⁶ In a study of adult patients receiving allogeneic bone marrow transplant, cyclophosphamide metabolism was also found to be variable and age dependent, but with no correlation to

disease-related outcome.²⁷ Interestingly, a recent study examined personalized administration of cyclophosphamide for pre-transplant conditioning based on kinetics of an initial dose; patients with individualized dosing experienced less nephrotoxicity and no difference in disease-related outcome.²⁸ Examination of pharmacokinetic differences in alkylating agent metabolism by age, and possibly gender, in patients with RMS is worthy of consideration.

Lower rates of mucositis were experienced in reporting periods 2–4 as compared to reporting period 1, likely due to early radiation therapy administered to the majority (63%) of patients with parameningeal tumours in reporting period 1.²⁹ Mucositis was relatively more common in children greater than age 5, which could reflect under-reporting of this symptom in young children.^{30, 31}

Adolescents had significantly worse peripheral nervous system toxicity compared to younger children which is in keeping with differential drug clearance based on size.³² Vincristine and vinorelbine clearance is more rapid in children than adults who have a more than two-fold longer terminal half-life.³³ However, a more recent study failed to show a difference in vincristine pharmacokinetics between children and adolescents ages 1.3–17.3 years.³⁴ Weekly vincristine has been the backbone of IRS therapy for RMS and is based on impressive response rates to single agent seen both historically and in pre-clinical models.³⁵ The relative importance of weekly vincristine in the context of modern therapy which includes aggressive local control measures for all ages and histologies of RMS has not been addressed. From our data, we were unable to determine the exact dose modifications for vincristine in older adolescents; however, the total cumulative delivered dose did not differ significantly compared to that given to younger children. Of note, due to capping of vincristine as dictated by the protocol, all patients with a body surface area greater than 1.3 m² received 2 mg of vincristine. Effectively, this results in relative under-dosing of larger adolescents compared to younger children. The International Society of Pediatric Oncology Malignant Mesenchymal Tumor study (MMT 89), does not include weekly vincristine as part of their therapy, with somewhat similar overall survival to IRS-IV, albeit with other major differences in therapy.^{36, 37} A recent analysis from COG confirms that despite lower total cumulative dose by body size (due to dose capping at 2 mg), adolescents experience greater vincristine-related neurotoxicity compared to younger children.³⁸

Our analysis is limited by the non-standardized use of G-CSF, which may have contributed to differences in myelosuppression observed as not all patients received the drug. However, there is no reason to believe that the use of G-CSF was age-dependent. Furthermore, anemia and thrombocytopenia rates were also less in the older patients, suggesting that variable use of G-CSF is unlikely to explain the lower frequency of hematologic toxicity in older patients. Radiation-related toxicities were not compared by age, which may be especially important with the variation of histology and primary tumor site in adolescence; this could be addressed in a future confirmatory study. To address these limitations, a similar toxicity analysis is currently underway for patients treated on the more recent intermediate-risk RMS study, D9803, to confirm the IRS-IV findings.

We have shown that adolescents with RMS experience significantly less hematotoxicity compared to younger children on IRS-IV, despite receiving similar cumulative dose of drug. Thus, differences in drug handling may contribute to their poor outcome, which may be affected by gender and/or age. COG STS investigators are currently studying the age-dependent pharmacokinetics of cyclophosphamide. Therapeutic strategies that may be reasonable for younger children may not be directly extrapolated to adolescents. Future study designs should focus on individualizing the dose of alkylating agent based on differences in drug handling in order to improve survival for adolescents with RMS.

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Figure 1. Treatment Plan for IRS-IV Patients

Mesna 360 mg/m²/dose was given 15 minutes before I or 450 mg/m²/dose before C and then every 3 hours 3 × 3 after each I or C. Chemotherapy doses were reduced by 50% in patients younger than 1 year, if tolerated (nadir absolute neutrophil count < 500 neutrophils/mL and platelet count > 50,000 platelets/mL), increased to 75% and then 100%. Abbreviations: V, vincristine 1.5 mg/m² (2-mg maximum); A, dactinomycin 0.015 mg/kg/d (0.5-mg maximum daily dose), days 0–4; C, cyclophosphamide 2.2 mg/m², day 0; I, ifosfamide 1.8 mg/m²/d, days 0–4; E, etoposide 100 mg/m²/d, days 0–4. *No radiation for stage 1/2, group I, and all group II; randomized to 50.4 Gy conventional v 59.4 Gy hyperfractionated for group III. **No radiation for group I; 41.4 Gy conventional to group II.

Table 1

Patient Demographics

		Age Group										P value
		1-4		5-9		10-14		15+				
		n	%	n	%	n	%	n	%			
Total		267	41	191	29	120	18	79	12			
Gender	Male	143	39	116	31	70	19	40	11	0.31		
Treatment	VAC	87	39	71	32	33	15	31	14	0.52		
	VAI	90	42	57	27	46	21	22	10			
	VIE	90	41	63	29	41	19	26	12			
Site	PM	68	31	85	39	43	20	23	11	<0.0001		
	Head & Neck	48	41	43	37	19	16	7	6			
	Extremity	43	42	21	20	24	23	15	15			
	GU	63	65	11	11	14	14	9	9			
	Other	45	37	31	26	20	17	25	21			

Table 3

Incidence of AE by Reporting Period and OR of AE Compared to Reporting Period 1

		Reporting Period			
		1	2	3	4
N		648	619	593	565
Neutropenia	Incidence	74%	65%	69%	75%
	OR *	1	0.67	0.79	1.05
	P value *		<0.0001	0.03	0.62
Thrombocytopenia	Incidence	33%	30%	48%	55%
	OR *	1	0.89	1.94	2.61
	P value *		0.24	<0.0001	<0.0001
Anemia	Incidence	54%	47%	50%	49%
	OR *	1	0.75	0.82	0.77
	P value *		0.003	0.04	0.01
Mucositis	Incidence	25%	15%	13%	13%
	OR *	1	0.53	0.42	0.39
	P value *		<0.0001	<0.0001	<0.0001
Infection	Incidence	23%	20%	24%	25%
	OR *	1	0.83	0.96	1.06
	P value *		0.10	0.77	0.63
Peripheral nervous system toxicity	Incidence	9%	15%	13%	9%
	OR *	1	1.87	1.63	0.94
	P value *		<0.0001	0.002	0.75

* Odds of AE compared to reporting period 1.

Table 5

Odds Ratio of AE by Age when compared to Age 1–4 years

		Age		
		5–9	10–14	15–20
Neutropenia	OR	1.06	0.57	0.43
	P value	0.71	0.0001	<0.0001
Anemia	OR	1.08	0.85	0.41
	P value	0.58	0.35	<0.0001
Thrombocytopenia	OR	0.97	0.44	0.34
	P value	0.8	<0.0001	<0.0001
Peripheral Nervous System Toxicity	OR	1.73	2.80	4.18
	P value	0.022	<0.0001	<0.0001
Infection	OR	0.85	0.55	0.41
	P value	0.24	0.001	<0.0001
Mucositis	OR	2.34	2.99	1.46
	P value	<0.0001	<0.0001	0.17