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Age- Related Toxicity in Patients with Rhabdomyosarcoma: A Report from the Children's Oncology Group

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Abstract

On the Fourth Intergroup Rhabdomyosarcoma study, older children experienced excessive neurotoxicity whereas younger children had increased myelosuppression. The purpose of this study was to determine whether the same pattern of toxicity was seen on the successor study when use of growth factor was required and dosing of chemotherapy was different by performing a retrospective cohort analysis on patients treated on Children's Oncology Group protocol D9803. Toxicity data were analyzed by stratifying children into four age groups. The frequency of grade 3/4 neurotoxicity, myelosuppression, infection and mucositis was predicted for each age group. The cumulative doses of vincristine and cyclophosphamide administered were measured as percent of protocol- prescribed dose. Adolescents (age 15+) were more likely to experience neurotoxicity compared to younger patients (OR 3.6, $P < 0.0001$). There was no difference in myelosuppression, infection or mucositis. The mean percent protocol-prescribed doses administered for vincristine and cyclophosphamide did not differ much by age group. Adolescents experienced more neurotoxicity with vincristine compared to younger patients. No differences in other toxicities were observed between age groups. Since adolescents received at least 85% of protocol prescribed doses of vincristine, it is difficult to attribute the poorer survival in this age group to inadequate protocol delivered therapy.

Keywords

rhabdomyosarcoma; age; toxicity; chemotherapy; neurotoxicity; mucositis; neutropenia

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Introduction

Rhabdomyosarcoma is the most common soft tissue sarcoma in children and adolescents. Cure rates for patients with non-metastatic rhabdomyosarcoma have improved from 25% in 1970 to 75% currently ¹. Chemotherapy-associated toxicities are a major factor contributing to morbidity. Therapy-related toxicities have been postulated to be associated with outcome and survival ². Differences in toxicity patterns by age have been observed, where older children and younger children experience certain toxicities with similar agents at different frequencies ²⁻⁴. In the Children's Oncology Group (COG) trial D9803, children under 3 years experienced higher hepatotoxicity when compared to older patients. The hepatotoxicity was associated with dactinomycin when dactinomycin was dosed on the basis of body surface area in children less than 3 years of age. This led to dose reduction of approximately 25% for those children at highest risk of hepatotoxicity ⁵. On the Intergroup Rhabdomyosarcoma Study IV (IRS IV), adolescents (15–20 years) experienced higher neurotoxicity, 5–9 and 10–14 age groups experienced more mucositis when compared to the younger group (1–4 years) whereas patients 5–9 years old experienced higher rates of hematological toxicity ². Our study was designed to validate the results of the previous study, as there were a few differences between patients treated on IRS IV and those treated on D9803. In contrast to IRS IV, D9803 did not use ifosfamide or etoposide, administered dactinomycin over one day instead of fractionated over 5 days, and required granulocyte colony stimulating factor as supportive care.

Methods

The study was designed as a retrospective cohort analysis in children treated on COG protocol D9803 for intermediate-risk rhabdomyosarcoma, from September 1, 1999 through August 5, 2005. The protocol had been approved by the institutions' ethics committees and patients and/or parents had signed appropriate informed consent for participation on D9803. There were 617 patients assessed in the primary analysis. This group was used for the analysis reported here. Details of treatment and outcome have been published previously ¹. There were 264 patients were randomized to Regimen A-VAC (vincristine, actinomycin and cyclophosphamide); 252 patients randomized to Regimen B-VAC alternating with VTC (vincristine, topotecan and cyclophosphamide). There were 101 patients with parameningeal primary tumors with intracranial extension, assigned to VAC non-randomly and immediate radiation therapy (Regimen C). We excluded 18 infants (under 1 year) because dosing methods for infants changed several times ⁵, and; data were missing for 1 patient. Toxicity data for 598 patients treated on this protocol were reviewed.

This trial used National Cancer Institute's CTC version 2.0 (Common terminology criteria for adverse events) for reporting toxicity and adverse events. There were 4 reporting periods during the treatment period. Toxicity data were collected during every reporting period. Reporting period (RP) 1 was from week 0 through 3, RP 2 was 3 through 12, RP 3 was 12 through 24 and RP 4 was 24 through 42. Only Grade 3 and 4 toxicities were reported. Data analyzed specifically for this report included neurotoxicity (motor and sensory), myelosuppression (neutropenia, lymphopenia, anemia and thrombocytopenia), oral mucositis, and infections. Hepatotoxicity was not re-evaluated because that has been

previously reported⁵. All toxicities were recorded as binary variables during each RP. Doses of vincristine and cyclophosphamide administered were analyzed for each age group during each of these periods, as well as the cumulative dose for each age group at the completion of therapy. Details of the dosing are provided in Table I. Exact details of the regimens been published previously¹.

Statistical Considerations

The primary outcome measure was the frequency of the toxicities in the different age groups. Secondary outcome measures included percentage of expected dose of protocol specified chemotherapy administered to all subjects. Patients were divided into groups based on age in years: 1–4, 5–9, 10–14 and 15+. The age group 1–4 was the reference group.

The rate of adverse events (AE) was modeled as a function of patient age in 4 groups. Generalized estimating equations with a binominal distribution and logit link were used to assess the presence of each first AE adjusted for sex, RP and treatment (2 treatments, VAC versus VAC/VTC) while correcting for correlation of patient data across the study periods. This method permitted the sample size to differ by reporting period, as patients' data were available. From modeling results, estimates of odds ratio of AE in various age categories were compared with the reference age group 1–4. In secondary models we assessed interaction between age and RP.

Cumulative doses were calculated as percentages of the protocol- prescribed dose. Doses were calculated for patients who completed all cycles of chemotherapy during the duration of the study. Both body surface area as well as capped doses were calculated and compared to the prescribed dose. All variables with P value of less than .05 were considered significant.

Results

Patient Demographics

There were 598 patients in this analysis. Their demographics are summarized in Table II. The highest percentage of children was in the 1–4 year age group (45%) followed by 5–9 (26%), 10–14 (26%) and 15+ (16%). There was a slight male preponderance (62%). The parameningeal (PM) site was the most common site in all the age groups (30%).

Toxicities

Neurotoxicity—Patients older than 15 experienced the most neurotoxicity, OR 3.6 (95% CI 2.19 to 6.06) $P < 0.0001$. Neurotoxicity continuously increased across RPs, with rising OR from 1.54 in RP1 to 3.64 in RP 4. The least amount of neurotoxicity was observed in the 1st RP while the most was seen in the 3rd RP. No difference between regimens or sexes was observed.

Neutropenia—There was no difference in odds ratio of neutropenia in the different age groups (Table III). Similar OR for neutropenia were observed in RPs 2, 3 and 4 (Table IV). There was no statistically significant difference in neutropenia between the regimens or sex.

Thrombocytopenia—No difference in thrombocytopenia was noticed between the groups (Table III). Higher rates of thrombocytopenia were observed in the third and fourth RP (Table IV). There was no difference in the rates of thrombocytopenia between the 3 regimens.

Anemia—Patients age 15+ had lower OR of anemia compared to the other groups (Table III). The lowest rates of anemia were seen in the 1st RP, which was also the shortest period. The highest rate of anemia was seen in the 4th RP, frequency of 44%, OR 6.2 and $P < 0.0001$ (Table IV). There were no differences between regimens or sex in the rates of anemia.

Infection—Patients older than 15 years had the lowest risk of infections, with an OR 0.3 (95% CI 0.2–0.4) $P < 0.0001$ (Table III), with patients age 10–15 also having a lower risk of infection compared to age 1–4, although not as low as those older than 15. The infection rate (with and without neutropenia) was the least in the 1st RP when compared across all age groups. The rates were similar within the next 3 RP's. There was no difference in the rates of infections between the 3 regimens or sex.

Mucositis—No difference in mucositis between the different age groups was found (Table III). The least amount of mucositis was observed in the 1st RP, while the highest amount was seen in the 2nd and 3rd RP (95% CI 0.7–1.8 and 0.7–2.00 $P < .0001$) (Table IV). Regimen C with VAC and early administration of radiotherapy demonstrated the largest amount of mucositis, with an OR of 4.1 (95% CI 2.44–7.19) $P < 0.0001$.

Chemotherapy Doses

Cumulative Dose of Cyclophosphamide and Vincristine—The cumulative dose administered per body surface area was analyzed at the completion of therapy. The percent-prescribed dose of cyclophosphamide was analyzed for the 3 regimens. Doses for patients who received chemotherapy throughout the study period were analyzed. Regimen A and C had similar prescribed doses of 30.8gm/m², whereas regimen B had a lower prescribed dose of 25.1gm/m², (20%) due to use of concurrent topotecan. Normalized doses were used as denominators (expected dose) to calculate the percent of protocol specified dose administered. In regimens A and C the range of prescribed dose administered for all the age groups was 86%–96% while for regimen B it was 90%–93% of the protocol specified dose (Table V).

Doses of vincristine were calculated using 45mg/m² as the normalized dose. This was used as the denominator for calculating the percent of the protocol specified dose. For patients with a high BSA, who had dose capped at 2 mg, a cumulative dose of 60mg was used as the normalized dose. Despite the higher risk of neurotoxicity, the majority of patients with neurotoxicity received close to protocol specified doses. Details of cumulative doses and mean percent prescribed doses of vincristine are presented in table VI.

Discussion

Our results confirmed the findings reported from IRS IV that neurotoxicity risk is significantly higher in the age group older than 15 years. Subjects older than 15 years had

more than twice the likelihood of neurotoxicity compared to any younger age group. Vincristine-associated neurotoxicity in adolescents has been reported in other studies as well. In patients with medulloblastoma higher neurotoxicity was noted in the adolescent age group. Due to this finding some authors recommend dose modifications for this specific age group ⁶. In a study investigating vincristine pharmacokinetics, the authors questioned if vincristine pharmacokinetics were age dependent. They found no correlation of age and vincristine pharmacokinetics, including elimination half-life, and volume of distribution.

Most patients over 10 years of age have reached a BSA of over 1.33m^2 , which subjects them to "dose capping", therefore these patients receive a lower dose of drugs per BSA when compared to those under 10 who also have a smaller BSA. Some authors argue against dose "capping" for the adolescent age group, based upon their findings of the lack of correlation between pharmacokinetics and age ⁷. In their study of vincristine pharmacokinetics, toxicity was not a variable; they did not evaluate age-based differences in toxicity. Despite the fact that younger patients, with smaller BSAs, receive higher doses of vincristine (when calculated by actual BSA) as compared to older patients subject to the dose cap, we cannot recommend elimination of "dose capping" due to the higher rate of neurotoxicity in older patients. In our study, the cumulative mean dose of vincristine for the younger patients in the 1-4 year range was $40.3\text{mg}/\text{m}^2$, whereas the calculated BSA dose for those in the age group 10-14 was $34\text{mg}/\text{m}^2$ and 15+ was $30\text{mg}/\text{m}^2$. The dose administered was also slightly higher for the 1-4 age group due to amendments in the protocol as there were patients whose doses were calculated by mg/kg ($0.05\text{mg}/\text{kg}$) as well as by body surface area ($1.5\text{mg}/\text{m}^2$).

Despite the higher likelihood of neurotoxicity adolescents still received at least 85% of protocol specified dose. There could be many reasons for this. Interruption of vincristine administration and re-initiation with 50% dose reduction was recommended by protocol for those experiencing severe peripheral neuropathy and paralytic ileus. This could explain the higher neurotoxicity observed in the 3rd RP compared to the 4th. The protocol did not recommend dose reduction for milder toxicities such as constipation and deep tendon reflex abnormalities. Even when vincristine dose was reduced often times it was successfully re-initiated once toxicity resolved.

A recent study evaluating genotypic factors, especially CYP3A5 expression and risk of vincristine-associated neurotoxicity, found that children with less vincristine induced peripheral neuropathy expressed CYP3A5 and produced more M1 (active metabolite) as compared to those not expressing CYP3A5. The active metabolite M1 concentration is inversely related to the severity of neuropathy ⁸. Also developmental differences in expression of CYP3A have been identified ^{9, 10}. These are age- dependent with higher levels expressed during the earliest years of life. There may be differing pharmacodynamics effects by age, yet to be understood.

In contrast to the study by Gupta et al conducted in patients treated on the IRS IV, where more myelosuppression was observed in the younger age (5-9 years) ², we did not observe age related differences in neutropenia or thrombocytopenia. This could be due to the consistent use of filgrastim in D9803 patients, as opposed to IRS IV. Another reason could be the additive myelosuppressive effect of etoposide and ifosfamide as used in IRS IV. The

total dose of cyclophosphamide was not significantly different in the two studies. In D9803 the total dose of cyclophosphamide was 30.8 g/m² for those randomized to VAC as compared with 25.1 g/m² on the VAC/VTC regimen, whereas on the IRS IV study, it was 26.4 g/m² for those randomized to VAC. We analyzed the cumulative dose of cyclophosphamide for all the age groups. The mean percent prescribed dose of cyclophosphamide administered for all the age groups in the 3 regimens was > 90% indicating that no major dose modifications occurred due to toxicity.

Infectious complications with and without neutropenia were least in the 10–14 and 15+ groups. No differences were noticed between the different regimens. Infectious complications increased progressively across RPs when compared to RP 1.

In contrast to the findings of Gupta et al, we did not find a difference in the rate of mucositis by age group. One of the reasons for not observing a difference in mucositis could be use of filgrastim. Filgrastim has been shown to be potentially beneficial for the prevention of mucositis in adults although the level of evidence is not strong ¹¹.

Contrary to some reports which suggest that some chemotherapy toxicities such as ototoxicity, cardiotoxicity and myelosuppression differ by gender^{13, 14, 15, 2, 16}, we found no such association in the toxicities we examined. Clearly more work needs to be done in understanding the role of gender, drug metabolism and toxicity.

Age is an independent prognostic factor and patients older than 10 have lower rates of failure free survival (FFS) of 53%, as compared to those in the 1–9 age group, with 72% FFS ¹². This poor prognosis is not explained by the unfavorable risk factors of histology, site, stage or group. It has been postulated that there are biological differences in the tumor itself among the different age groups ¹². The higher frequency of therapy- related toxicity could cause delays in treatment and lower dosing of agents. We have shown that adolescents did not suffer from significant dose reductions in comparison to younger patients. However, based on our findings, we do not recommend an increase in the dose of vincristine in the adolescents, as they are likely to experience neurotoxicity, whereas reduction of dose could lead to risk of relapse.

A major limitation in this study is its retrospective nature. In addition, drug interactions have recently been highlighted as important factors in drug toxicity¹⁷, and these could not be evaluated due to the lack of data on concomitant medications received by patients. Moreover, assessment of chemotherapy dose was challenging for the youngest patients due to multiple protocol amendments since patients were dosed by 2 different methods of dose calculation. We were not able to analyze differences in dose intensity between the age groups because of lack of available data on dates of chemotherapy administration. The risk of neurotoxicity was highest in the 15+ age group, with the OR 3.6 $P < 0.0001$, when compared to younger patients. There were no differences in the risk of thrombocytopenia or neutropenia between the different age groups. The majority of patients received protocol prescribed doses of cyclophosphamide and vincristine. It is possible that the poorer outcome seen in older patients is related to the higher risk of vincristine -associated neurotoxicity, as it precludes further dose escalation of this agent. A recent review has highlighted the

importance of understanding pharmacogenomics in order to rationally dose adjust chemotherapeutic agents. It points out that unfortunately no genetic variants have been conclusively validated to be related to vincristine induced neuropathy. Hopefully with ongoing research efforts this will change for many drugs¹⁸.

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Table I

Dosing by age groups on D9803

Age	Vincristine	Dactinomycin	Cyclophosphamide	Topotecan
3 Years	1.5mg/m ² Max dose 2.0mg	0.045mg/kg one dose max dose 2.5mg	2.2g/m ² IV	0.75mg/m ² /day for 5 days
1 year <3 Years	0.05mg/kg Max dose 2.0mg	0.045mg/kg one dose max dose 2.5mg	73mg/kg/dose	0.75mg/m ² /day for 5 days
<1 Year	0.025mg/kg	0.025mg/kg one dose	36mg/kg	0.75mg/m ² /day for 5 days

Dosing for VAC (vincristine, dactinomycin, cyclophosphamide) arms. For patients on VTC (vincristine, topotecan, cyclophosphamide) cycles, Cyclophosphamide was 250 mg/m²/day for 5 days when given with Topotecan

Table II

Patient characteristics based on tumor location

Site	1–4 Years (n =268) *	5–9 Years (n =157) **	10–14 Years (n =97) ***	>15 Years (n =76) ****
PM	64	51	43	20
PM extension	12	14	5	5
Extremity	38	18	21	10
GU B/P	61	18	3	8
GU non-B/P	7	8	7	13
Orbit	6	6	2	2
Retroperitoneum	38	21	7	2
Perineum	4	5	0	5
Trunk	7	5	3	0
Head and Neck	17	4	5	4
Other	11	6	0	5

PM: Para -meningeal, GU: genitourinary, BP: bladder/prostate

* Missing data 4,

** Missing data 1,

*** Missing data 1,

**** Missing data 1

Table III

Odds Ratio of Adverse Events by Age compared to the reference age group (1-4 years)

Adverse Event	1-4 (n=268)	5-9 (n=157)	10-14 (n=97)	15+ (n= 76)
Neutropenia				
OR (95%CI)	1	0.9 (0.7 – 1.3)	1.08 (0.7 – 1.6)	0.89 (0.6 – 1.3)
P		0.84	0.65	0.62
Thrombocytopenia				
OR (95%CI)	1	1.07 (0.7 – 1.5)	1.2 (0.8 – 1.8)	0.7 (0.4 – 1.14)
P		0.69	0.34	0.16
Anemia				
OR (95%CI)	1	0.99 (0.7 – 1.4)	1.00 (0.7 – 1.4)	0.6 (0.4 – 1.0)
P		0.96	0.96	0.03
Mucositis				
OR (95%CI)	1	1.18 (0.7 – 2.0)	1.59 (0.9 – 2.7)	1.27 (0.6 – 2.8)
P		0.56	0.09	0.55
Infection				
OR (95%CI)	1	0.9 (0.7– 1.8)	0.56 (0.4– 0.8)	0.34 (0.2– 0.4)
P		0.46	0.0006	<0.0001
Neurotoxicity				
OR (95%CI)	1	1.53 (0.9–2.4)	1.6 (0.9–2.7)	3.64 (2.1–6.06)
P		0.063	0.08	<0.0001

Table IV

Odds Ratio of Adverse events by reporting periods (RP) compared to the reference group (RP1)

Adverse Event	RP 1	RP2	RP3	RP4
No of Patients	564	574	530	511
Neutropenia	198 (35%)	266 (46%)	245 (46%)	240 (47%)
OR 95% CI	1	1.6 (1.3–2.0)	1.6 (1.2–2.0)	1.6 (1.3–2.0)
P		<0.0001	<0.0001	<0.0001
Thrombocytopenia	56 (9%)	137 (24%)	172 (32%)	220 (43%)
OR 95% CI	1	3.0 (2.0–3.9)	4.3 (3.1–6.0)	6.8 (4.9–9.5)
P		<0.0001	<0.0001	<0.0001
Anemia	63 (11%)	214 (37%)	188 (35%)	225 (44%)
OR 95% CI	1	4.7 (3.4–6.4)	4.3 (3.1–6.0)	6.2 (4.5–8.5)
P		<0.0001	<0.0001	<0.0001
Mucositis	13 (2%)	43 (7%)	43 (8%)	22 (4%)
OR 95% CI	1	3.4 (1.8–6.4)	3.7 (1.9–7.6)	1.9 (0.9–3.8)
P		<0.0001	<0.0001	<0.0001
Infection	217 (38%)	266 (46%)	245 (46%)	240 (47%)
OR 95% CI	1	2.0 (1.4–2.3)	1.9 (1.4–2.4)	2.3 (1.8–2.9)
P		<0.0001	<0.0001	<0.0001
Neurotoxicity	19 (3%)	63 (11%)	92 (17%)	63 (12%)
OR 95% CI	1	3.5 (2.0–5.9)	6.0 (3.6–10.0)	4.0 (2.4–6.8)
P		<0.0001	<0.0001	<0.0001

Table V

Cumulative Dose of Cyclophosphamide by age group and regimen

Age Group	Regimen	Number of Observations	Mean Dose g/m ² (cumulative)	Mean% prescribed Dose	Standard Deviation
1-4	A	95	28	90%	33.7
	B*	85	23	93%	22.6
	C	24	29	93%	29.7
5-9	A	41	30	96%	25.6
	B*	54	23	93%	24.2
	C	34	29	95%	22.5
10-14	A	33	29	94%	26.8
	B*	32	24	94%	19.7
	C	18	29	93%	30.9
15+	A	20	29	96%	21.4
	B*	23	23	92%	25.5
	C	8	27	86.4%	42.3

* Cumulative dose of 25.1 g/m² for regimen B compared to 30.8 g/m² for regimen A

Table VI

Cumulative Dosing of Vincristine by Age Group and Dose Capping

Age Group	Number of Observations	Cumulative Mean Dose (mg/m ²)	Mean % prescribed Dose	Standard Deviation
1–4	205	40.3	90%	5.57
5–9	130	41.3	92%	5.9
10–14	31	41.4	92%	4.4
10–14 *	62	51.3	85%	9.8
15+ *	51	52.4	87%	12.1

* Patients received capped dose of 2mg with a maximum dose of 60mg versus 45mg/m² for all patients who did not receive capped dose.