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Dactinomycin and Vincristine Toxicity in the Treatment of Childhood Cancer: A Retrospective Study from the Children's Oncology Group

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Abstract

Background—Dactinomycin (AMD) and vincristine (VCR) have been used for the treatment of childhood cancer over the past 40 years but evidence-based dosing guidance is lacking.

Methods—Patient AMD and VCR dose and drug-related adverse event (AE) information from four rhabdomyosarcoma (RMS) and two Wilms tumor (WT) studies were assembled. Statistical modeling was used to account for differences in AE data collection across studies, develop rate models for grade 3/4 CTCAE v3 hepatic- (AMD) and neuro- (AMD) toxicity, assess variation in toxicity rates over age and other factors, and predict toxicity risk under current dosing guidelines.

Results—For the same dose/body size, AMD toxicity rates were higher in patients <1 year than older patients and VCR toxicity rates increased with age. The statistical model provided estimates for AMD and VCR toxicity risk under current dosing schedules and indicated that patients of smaller body size were at lower risk of VCR toxicity than larger patients of the same age. The rate of AMD toxicity was highest early in treatment and was lower in patients who tolerated initial AMD without toxicity.

Conclusion—The observed decrease in AMD toxicity rate with cumulative dose may indicate sensitivity in a subgroup of patients while the observed increase in VCR toxicity risk with age may indicate changing sensitivity to VCR. Current dosing practices result in a fairly uniform toxicity profile within age group. However, PK/PD studies should be done to provide further information on best dosing guidelines.

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Potential conflicts of interest

Dr. Skolnik is an employee of AstraZeneca, and own shares in AstraZeneca.

Keywords

hepatic toxicity; neuropathy; rhabdomyosarcoma; risk estimation; Wilms tumor

Introduction

Finding a balance between providing sufficient therapy and avoiding life-threatening toxicity is critical when treating potentially curable diseases such as pediatric cancers. Dactinomycin (AMD) and vincristine (VCR) are two anti-cancer agents that have been used together to treat children with Wilms tumor (WT) and rhabdomyosarcoma (RMS) for over 40 years. Little is known about PK/PD relationships in children, resulting in risk of toxicity and arbitrary dose reductions. Evidence-based dosing guidance is lacking, resulting in apparent inconsistencies across age and type of cancer in dosing strategies.(1, 2) (Supplemental Tables I and II). For example, consider three year old children of median height and weight enrolled in these studies. The AMD dose per cycle would have been between 0.6 mg and 1 mg, depending on whether the diagnosis was WT or RMS and depending on the version of the protocol. The weekly dose of VCR would have been 0.9 mg for patients with WT but 0.7 mg for RMS patients. Similar discrepancies exist for other ages. Toxicities of AMD include myelosuppression, mucositis, and hepatotoxicity, as well as sinusoidal obstruction syndrome (SOS), which carries a high risk of death.(3, 4) VCR is associated with peripheral neuropathy, characterized by progressive motor, sensory, and autonomic involvement. In the absence of predictive data, clinicians are left with the challenging task of optimizing therapy.

This report provides results from the first project of a larger Best Pharmaceuticals for Children's Act (BPCA)-funded study of AMD and VCR in children with cancer (<http://bpca.nichd.nih.gov/>). The goal of the project is to provide additional labeling data for these two agents by providing both analyses of dose-exposure (PK) and exposure-response-toxicity (pharmacodynamic; PD) data from both completed and ongoing studies of the Children's Oncology Group (COG). Here we present a retrospective analysis of historical dose-exposure/toxicity data from several completed studies. Our objectives were to identify clinical trials with dose/toxicity data that were adequate for assessing toxicity risk; estimate age-specific risk of AMD and VCR toxicity from the assembled data; estimate toxicity risk based on dosing schedules currently in use; and assess the mechanisms of heterogeneity of risk to serve as background for a prospective BPCA COG study.

Materials and Methods

We performed a retrospective analysis of patients who participated in selected clinical trials conducted by the Children's Cancer Group, the Pediatric Oncology Group, and the COG, between the years 1986 and 2002. Selection criteria for the trials were: Use of AMD and VCR in the planned treatment; available complete and standardized records containing AMD and VCR doses; recording of type of adverse event (AE) and cumulative drug dose at the time of AE; and recording of age, weight, and height or BSA at diagnosis. Six trials met these criteria, details are available at <http://www.clinicaltrials.gov>:

IRS-IV was a randomized trial that opened in October 1991 and enrolled 883 previously untreated children with RMS or undifferentiated sarcoma, comparing three treatment regimens: VAC (VCR + AMD + cyclophosphamide; CPM), VAI (VCR + AMD + ifosfamide), and VIE (VCR + ifosfamide + etoposide) (4).

D9602 was a randomized trial that opened in September 1997 and enrolled 399 patients with newly diagnosed low-risk embryonal/botryoid RMS to evaluate treatment using VCR and AMD with or without CPM and radiation.

D9802 was an upfront “window” trial of VCR and irinotecan followed by multi-agent therapy that opened in September 1999 and enrolled 110 patients, and included VAC for newly diagnosed stage 4/clinical group IV RSM patients.

D9803 was a randomized phase 3 trial that opened in September 1999, and enrolled 635 patients <21 years with intermediate-risk RMS. Patients were randomly assigned to VAC or alternating VAC with VCR, topotecan and CPM (VTC), with the exception of patients requiring immediate radiation therapy who were non-randomly treated with VAC.

NWTS-4 opened in August 1986 and enrolled 1638 WT patients <16 years who were treated with VCR and randomized to receive either divided dose or pulse-intensive AMD and short duration or long duration of therapy (5, 6). Electronic data entry was suspended part-way through this study. There was considerable variability in the way dose information was recorded in the medical records and it was decided to only include patients who had computerized drug dose information and met the criteria described above.

NWTS-5 opened in June 1995 and included 2800 patients <16 years old with stage I-V favorable histology WT, stage I-V focal or diffuse anaplastic WT, or stage I-V clear cell sarcoma of the kidney and rhabdoid tumors. Treatment regimens depended on recurrence risk and consisted of combinations of surgery, chemotherapy and radiation therapy. All chemotherapy regimens included VCR and other agents (AMD, doxorubicin, CPM, etoposide) depending on the histology and stage of the tumor. Dates of adverse events (AE) and dose information were reported only on paper forms. Because the records were consistent and uniform throughout the study, abstraction of paper case report forms (CRFs) was performed to obtain the date of selected AMD and VCR-related adverse events, as well as doses of VCR or AMD.

Patients from these studies were required to be under 21 years old, to have recorded age at diagnosis, weight, dose, and complete toxicity information for both AMD and VCR to be included in the analysis.

Dose and adverse event information

The protocol-specified drug dosages are given in Supplemental Tables I and II. However, the actual amount of drug administered to the patient, as recorded in the patient treatment roadmap, was used for this data analysis. For all studies but NWTS-5, dose and AE computerized data were summarized by course/phase, of which there were typically four. Dose was reported as total AMD and VCR (mg) received during the specified course/phase. Reported AEs were similarly summarized and recorded by course/phase. For NWTS-5, AMD and VCR dose for each week of treatment, and reported AEs, were abstracted from paper records.

AMD and VCR dosage was determined based on body size, either by patient weight or BSA. Thus, dose summaries were calculated from the course/phase dose data as cumulative dose/kg of body weight and cumulative dose/m² of BSA.

The detail with which AEs were recorded varied across the studies. IRS-IV, D9602 and NWTS-4 collected data on fewer adverse events, defined by study-specified criteria, than other studies. NWTS-5 used a more extensive list of study-defined AEs, while the NCI Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3.0) grade 3 and

4 AEs were reported for D9802 and D9803. The pre-defined lists of study-specific AEs related to VCR or AMD are given in Supplemental Tables III and IV, along with the number of patients who experienced each toxicity. A “VCR or AMD toxicity event” was defined as the occurrence of one or more recorded AE from this list. For example, because AMD causes hepatotoxicity, AEs related to hepatotoxicity, such as large elevation in AST (SGOT)/ALT (SGPT) were considered “AMD toxicity event(s).” Similarly, because peripheral neuropathy is associated with VCR, AEs uniquely related to neuropathy, such as “foot drop,” were considered “VCR toxicity event(s).” Only severe or life threatening occurrences of these AEs were included in the toxicity event determination. No further determination of causality of toxicity was performed.

Statistical methods

The goals of the statistical analysis were two-fold. The first was to build a model that accounted for study differences to describe risk of toxicity as a function of age and dose, using the COG clinical trials data. The second was to use the model to estimate the risk of AMD and VCR toxicity under dosing guidelines used in current WT and RMS studies. In order to avoid the complications that arise when assessing multiple toxicity events in a single patient, the outcome variable was the first toxicity event, i.e., the first study-specific AMD (VCR) AE of those listed in Supplemental Table III (Supplemental Table IV). Thus, the relevant data for analysis was cumulative dose (mg/kg or mg/m²) at the first AE event for patients experiencing toxicity, or cumulative dose at end of treatment for patients not experiencing toxicity. An AMD toxicity event did not “censor” VCR dose and vice-versa. Modeling techniques were used to account for the difference in level of AE reporting across studies. Specifically, for each drug, the rate of first toxicity event was modeled in a Cox regression (7) as a function of dose (d), age group (a), and study (s) as $\lambda(d, a, s) = \lambda_a(d) \exp(\beta_s)$. The model assumed that the AE reporting differences resulted in a proportional difference in toxicity rates between studies. The influence of sex, race, and body size (weight or BSA) on toxicity rates, after accounting for age, was assessed by the likelihood ratio test for inclusion of the factor into the regression model. Estimation of the probability of toxicity within study and age group as a function of cumulative dose measures was done using the generalization of the Kaplan-Meier survival curve for proportional hazards models (8).

In current WT and RMS studies, CTCAE v3.0 is being used for AE coding. Because D9803 is a recent study that reported grade 3 or 4 CTCAEv3 hepatic and neurologic AEs, age-specific toxicity risk, as estimated for D9803 by the Cox regression models, were used to predict risk of toxicity under current dosing guidelines. Specifically, the predicted toxicity risk was estimated as the toxicity risk estimated from the Cox regression at the planned total cumulative dose/kg or m². Except for patients <1 year old, it was assumed that the dosing schedule at age of diagnosis applied for the entire treatment. For patients <1 year, doses were computed at a diagnosis age such that patient’s induction dose is received at age <1 year, and that the age 1–2 year dosing was given thereafter. For patients ≥12 years, the predicted toxicity risks were computed over a range of body sizes to take into account capping of dose.

To investigate whether the rate of first toxicity varied with increasing dose, the rate as a function of cumulative dose/kg was estimated in 0.1 mg/kg intervals using Poisson regression (8) and the pattern of toxicity rates was examined. Ninety-five percent confidence intervals (95% CI) were computed for the estimated toxicity rates using the Wald method (8).

Because this study is descriptive rather than hypothesis-based, formal statistical testing was not done. However, p-values from statistical tests were used to provide a measure of the degree to which the data supported variation in toxicity rates across a given factor.

Results

In a total of six clinical trials, 4567 patients met the inclusion criteria for complete data. Of these, 286 (6%) experienced AMD-related toxicity and 583 (13%) experienced VCR-related toxicity as defined by our methodology. Table I gives the total number of patients meeting the inclusion requirements and the number of patients with VCR and AMD toxicity by study, sex, race, ethnicity, and age. The mean total cumulative AMD dose among toxicity-free patients were 0.34 mg/kg and 8.7 mg/m² while the VCR means were 0.94 mg/kg and 23.5 mg/m². There was considerable variation across study and age group; see Supplemental Tables V and VI. In particular, WT patients received much lower total cumulative doses than RMS patients.

Probability of toxicity as a function of age

There was evidence of variation in toxicity by age for both AMD and VCR. Nearly all of age-variation in AMD toxicity rates as a function of dose/kg can be attributed to the <1 year age group being at higher toxicity risk than all other age groups ($p=0.005$ for age <1 vs. 1 years). After accounting for the <1 age group, there is no evidence of a difference between the other age groups ($p=0.84$). The results are similar with toxicity expressed as cumulative dose/m². Supplemental Figures 1 and 2 respectively show estimated CTCAEv3 grade 3 or 4 AMD probability of toxicity as a function of cumulative dose/kg and of dose/m² by age group based on the Cox regression analyses.

There was a steep increasing trend in VCR probability of toxicity with increasing age for a given dose/kg or dose/m² ($p<0.001$), with no evidence of a difference among patients <1 year and patients 1–2 years old (Supplemental Figures 3 and 4).

Probability of toxicity by gender, race, ethnicity, and body size

There was no evidence of variation in AMD or VCR toxicity rates across gender, race or ethnicity ($p>0.10$ for all tests). After accounting for age, there was no evidence of variation in rate of AMD toxicity by weight or BSA at diagnosis. For VCR, except for patients 16 years, the average rate of toxicity in patients in the lowest quartile of weight or BSA for their age was approximately 75% lower than in larger patients ($p=0.002$ and $p=0.09$ for dose/kg and dose/m², respectively).

Predicted AMD and VCR toxicities given current dosing guidelines

Table II summarizes the AMD and VCR treatment plans for currently open COG RMS trials and for Regimen DD-4A in WT studies. Other WT regimens are similar with respect to AMD and VCR dosing. While the amount of drug per dose are similar for RMS and WT patients, RMS patients receive much more total AMD and VCR than WT patients because of the greater number of doses. All AMD doses, and VCR doses for patients <3 years, are based on weight (mg/kg). VCR dosing for children 3 years is based on BSA (mg/m²). All of the treatment plans specify dose caps (Table II). The dose caps of AMD (2.5 mg; 55.6 kg) and VCR (2 mg; 1.3 m²) apply to almost half of the patients age 12–15 years, and to almost all patients 16 years or older.

Table III gives the predicted toxicity risk for currently open studies based on the models derived using retrospective study data as described above. In general, WT studies specify lower AMD and VCR doses than RMS studies and thus the predicted toxicity probabilities

are correspondingly lower. Further, capping of dose applies primarily to older patients and, for patients of the same age, a decrease in predicted toxicity with increasing body size is observed. For AMD, there is little variation of toxicity risk over age group and body size over the range of doses that patients receive with an overall predicted hepatic toxicity risk of approximately 10% for WT studies and 15% for RMS studies.

For VCR, there is a large range of predicted neurotoxicity probabilities over age, with older patients at approximately double the risk of the youngest patients. Given the dosing schedule for treatment of WT, the predicted neurotoxicity increases steeply from 7.3% in patients aged <1 year to 30% in patients 3–11 years and ranges from about 25–40%, depending on the size of the patient, for patients aged ≥12 years. For RMS patients <3 years, the risk of neurotoxicity is about 25%, while for patients over 3 years, the predicted risk is estimated to be in the 50% range.

Rates of toxicity as a function of dose

The risk of first AMD toxicity associated with a given dose was highest early and decreased with the cumulative toxicity free dose/kg completed. For patients <1 year old at diagnosis, the predicted rate of AMD toxicity was 8.6% (2.7–27.3) per 0.1 mg/kg of dose up to a cumulative dose of 0.2 mg/kg. However, for patients who received a cumulative dose of >0.2 mg/kg without toxicity, the rate of first AMD toxicity decreased to 3.5% (0.9–13.6) per additional 0.1 mg/kg. For patients 1–11 years, the predicted rate was 4.3% (3.4–5.4) per 0.1 mg/kg up to 0.4 mg/kg, after which the rate dropped to 1.5% (0.9–2.4) per 0.1 mg/kg. For patients aged 12–16 years, the predicted rate was 4.6% (3.3–6.6) per 0.1 mg/kg up to 0.4 mg/kg, after which the rate dropped to 3.7% (1.6–8.5). A post-hoc test of constant first AMD rate with cumulative dose/kg was rejected in favor of a rate pattern in which there was a decrease ($p<0.001$).

In younger patients, there was no indication that rate of first VCR toxicity for a given dose varied with total dose/kg received. For patients aged <1, the estimated rate of first VCR toxicity was 1.0% (0.1–7.0) per 0.1 mg/kg and for patients aged 1–11 the rate was 3.5% (3.0–4.2) per 0.1 mg/kg, regardless of cumulative toxicity free dose/kg. For patients aged 12–16 years, there was evidence of an increase in rate from 3.5% (1.9–6.4) per 0.1 mg/kg up to 0.2 mg/kg after which the rate is 9.1% (7.4–11.4) per 0.1 mg/kg.

Discussion

This report represents a comprehensive analysis of both AMD- and VCR-related toxicity in pediatric cancer studies through the COG, focusing on factors that define risk relationships and prediction of toxicity risk under currently used treatment schedules. Current dosing practices are based on what has been shown to be efficacious for treating WT and RMS. WT patients receive lower doses of both AMD and VCR than RMS patients of a similar size and are predicted to experience less toxicity. Within a given age group and after accounting for body size in the cumulative dose measure (mg/kg or mg/m²) toxicity rates did not vary substantially over a range of the appropriate body size measure for both drugs. This is not surprising given that linear PK apply for both agents in this dose and age range.(9–12)

Our analysis indicated that the youngest patients are at much higher risk of AMD toxicity at a given cumulative dose/body size. This is in agreement with, and provides further validation of, early report of hepatopathy from D9803 (3). This finding was not due to inclusion of D9803 patients in our data set; the youngest patients were still found to be at much higher toxicity risk when D9803 patients were excluded from the analysis ($p=0.009$ for <1 vs. ≥1 years and $p=0.34$ after accounting for the <1 age group). Under current AMD dosing, toxicity risk is similar across patient age and body size: approximately 10% for WT

and 15% for RMS patients. The somewhat larger estimated risk predicted for a patient diagnosed at 6 months old (25%) has a large confidence interval and should not be over-interpreted. However, it may indicate that, even with the dose reduction after the D9803 toxicity report, that young patients are still at higher toxicity risk. Under the current treatment schedules, VCR toxicity risk increases with age, but is fairly constant over body size within age group. For RMS study dosing, about 50% of patients 12 are predicted to experience grade 3 or 4 CTCAE v3.0 neurotoxicity.

A key finding is that the risk of AMD toxicity drops in patients who do not experience toxicity with their initial dose of AMD. This pattern of AMD toxicity risk is consistent across study and age. Our findings do not support a cumulative effect of AMD on risk of toxicity although they do support a non-linear relationship between age and risk of toxicity, with children <1 year at greater risk for AMD-related toxic events. In contrast, we found evidence of increasing risk of VCR-related toxicity with cumulative dose of VCR in older children. Overall risk of VCR-related toxicity was related to increasing age. These findings may suggest that for AMD children <1 year are susceptible to hepatotoxicity. In addition, the finding that patients are more likely to experience AMD toxicity at lower cumulative dose/kg, rather than later in treatment, may suggest a susceptible patient population. However, to date no studies have been performed to identify these risk factors and further studies are necessary to determine whether there is a predisposition for AMD-related toxicity. This is consistent with the findings early in the D9803 study, where patients with SOS experienced this toxicity early in their treatment, specifically by the sixth week of treatment.(3) The absence of this finding for VCR may support an age- or dose-related relationship, rather than a susceptibility model, although current evidence may suggest otherwise(11–13). The rate of toxicity increased with cumulative VCR dose received in the 12–16 age group, but there was no evidence of such an association in younger patients.

One of the challenges in this analysis was that AEs recorded in different trials were not the same. This may have resulted in inaccurate compilation of AEs from earlier trials, either under- or over-representing AEs in these trials; an example of this is seen with the absence of the specific term veno-occlusive disease (VOD) or SOS in trial D9803. Other differences in studies, such as dose intensity, other treatment modalities used, or other supportive therapies, may result in study-related differences in toxicity rates. The statistical modeling strategy accounted for the study specific discrepancies to a large degree; however, it was not possible to separate out the reasons for study-specific differences.

It was not possible to account for some of patient-specific factors likely to influence susceptibility to toxicity. For example, patients who received radiation treatment involving the liver are thought to be more susceptible to AMD-associated hepatic toxicity from AMD; however it was not feasible to incorporate radiation field information in this study. Also, because the analysis did not take into account the fairly rare competing risks of relapse or death during the treatment period, the toxicity risk estimates may be slightly inflated.

Another consideration in the interpretation of our findings is that the attribution of specific AEs to drug toxicity is imprecise. For AMD, the AEs used to define AMD toxicity are sensitive, but not very specific, to actual AMD toxicity. In particular, AMD toxicity will very often result in elevated transaminases, however many other factors can lead to elevated transaminases. In contrast most of the AEs used to define VCR toxicity are fairly specific to VCR but are subjective and not always very sensitive. For instance, foot drop, a neuropathy that occurs in patients who are walking, will not be seen in an infant. Furthermore, cranial neuropathy may manifest as hoarseness however a hoarse cry in an infant may not be readily apparent. A possible explanation for the observed age dependence in VCR toxicity may be differential sensitivity of the AEs available to this study.(14, 15)

Although there were a large number of patients in our study, the number of toxicity cases is too small to precisely assess risk of toxicity in some subgroups. In particular, patterns of risk in <1 year old patients are of special interest but, out of the 316 patients <1 year in our study, there were only 24 AMD and 12 VCR toxicity cases so the confidence intervals are wide and there is little statistical power to identify patterns of risk for this age group. Another limitation of the data used in this study is that dose at toxicity occurrence is only approximately known. Because toxicity occurrence is reported during a given dose interval, the error due to granularity of dose is proportionally larger at low doses than at high doses. We used a number of statistical adjustments, including imputation based on similar patients, and mid-point interpolation. The results were qualitatively similar to those without adjustment. Unfortunately, as no exposure data was collected in these trials, dose remains the best surrogate for toxicity despite this imprecision.

In spite of these limitations, the large patient population created from pooling six clinical trials makes credible statistical analysis possible. No single study has sufficient numbers of patients to identify and estimate variation in toxicity risk. The proportional hazards modeling approach can account for differences across studies, including AE reporting methods and dosing schedules, by assuming that, within age group, the rates of toxicity as a function of cumulative dose per body size unit are parallel on a log scale. A global test of fit indicated that this assumption adequately describes the variation in rates across study.

Patient age and body size (either weight or BSA) have been the main determinants of treatment dose level. This motivated the choice of cumulative body size-normalized dose and age as the primary variables in our toxicity rate models and provided a natural basis for predicting toxicity risk given current dosing practices. The study data offers the opportunity to assess refinements or alternatives to current dosing strategies. For instance, it was found that for the same dose/m² VCR toxicity risk varied somewhat with BSA suggesting dosing guidelines could be refined to obtain a toxicity risk profile that is constant over BSA. However, assessment of a change in dosing practices needs to take into account potential changes in efficacy, and possibly of exposure, a subject of future work.

This study filled an important gap in knowledge by providing an initial pediatric prediction model for drug induced toxicities associated with AMD and VCR and provides mechanistic hypotheses for a current prospective study of PK/PD and pharmacogenetic relationships for these drugs, underway through the COG and sponsored by the BPCA, through the National Institutes of Health, in which many of the issues raised in this study will be addressed and answered in a prospective fashion.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Number of patients and toxicity cases by study and patient characteristics.

Study	AMD			VCR		
	Patients	Cases	Toxicity proportion	Cases	Toxicity proportion	Toxicity proportion
IRS-IV	525	58	11%	167	32%	
D9602	394	48	12%	95	24%	
D9802	62	15	24%	32	52%	
D9803	607	86	14%	224	37%	
NWTS4	636	40	6%	37	6%	
NWTS5	2343	39	2%	28	1%	
Sex						
Male	2331	162	7%	333	14%	
Female	2184	119	5%	226	10%	
Unknown	52	5	10%	24	46%	
Race						
Asian	306	10	3%	13	4%	
Black	686	29	4%	68	10%	
White	2739	170	6%	354	13%	
Other	69	2	3%	1	1%	
Unknown	767	75	10%	147	19%	
Ethnicity						
Hispanic or Latino	148	27	18%	40	27%	
Not Hispanic or Latino	1121	138	12%	301	27%	
Unknown	3298	121	4%	242	7%	
Age at diagnosis						
<1	396	24	6%	12	3%	
1–2	1287	63	5%	88	7%	
3–11	2454	151	6%	320	13%	
12–15	259	28	11%	96	37%	
16+	171	20	12%	67	39%	

Table II

AMD and VCR dosing for currently open COG RMS and WT trials (Regimen DD-4A). Single AMD dose is capped at 2.5 mg in RMS studies and at 2.3 mg in WT studies. Single VCR dose is capped at 2 mg for all studies.

AMD dosing	<1 yr	1 yr	Number of doses
RMS studies	0.025 mg/kg	0.045 mg/kg	12
WT DD-4A ^a	0.023 mg/kg	0.045 mg/kg	5

VCR dosing	<1 yr old	1–2 yrs old	3 yr old	Number of doses
RMS studies	0.025 mg/kg	0.05 mg/kg	1.5 mg/m ²	30
WT DD-4A (cycles 1–4) *	0.025 mg/kg	0.05 mg/kg	1.5 mg/m ²	10
WT DD-4A (cycles 5–9) **	0.034 mg/kg	0.067 mg/kg	2 mg/m ²	5

* Given weekly.

** Given every three weeks.

Table III

Predicted AMD and VCR toxicity by age and body size given dosing guidelines used in current studies.

Dactinomycin					
Age	Body size (percentile)**	WT studies*		RMS studies	
		Cumulative dose	Percent predicted hepatic-toxicity risk (95 % CI)	Cumulative dose	Percent predicted hepatic-toxicity risk (95% CI)
0.5	--	0.115 mg/kg	9 (3,14)	0.48 mg/kg	25 (12,36)
1–2	<55 kg	0.225 mg/kg	11 (7,14)	0.54 mg/kg	14 (10,19)
3–11	<55 kg	0.225 mg/kg	9 (7,12)	0.54 mg/kg	16 (13,20)
12–15	<55 kg (50th)	0.225 mg/kg	10 (5,15)	0.54 mg/kg	17 (10,24)
12–15	80 kg (90th)	0.156 mg/kg	6 (3, 10)	0.38 mg/kg	14 (8,20)
16+	<55 kg (10th)	0.225 mg/kg	11 (5,17)	0.54 mg/kg	18 (9,26)
16+	70 kg (50th)	0.179 mg/kg	10 (5,16)	0.43 mg/kg	15 (8,22)
16+	90 kg (90th)	0.139 mg/kg	8 (3,12)	0.33 mg/kg	15 (8,22)

Vincristine					
Age	Body size (percentile)**	WT studies		RMS studies	
		Cumulative dose	Percent predicted neurotoxicity risk (95 % CI)	Cumulative dose	Percent predicted neurotoxicity risk (95% CI)
0.75	--	0.42 mg/kg	7 (1,13)	1.18 mg/kg	24 (10,35)
1–2	<51 kg	0.84 mg/kg	18 (13,22)	1.5 mg/kg	26 (20,32)
3–11	<1.3 m ²	25.0 mg/m ²	30 (26,34)	45 mg/m ²	41 (36,45)
12–15	1.3 m ² (10th)	21.7 mg/m ²	39 (30,47)	45 mg/m ²	55 (45,64)
12–15	1.7 m ² (50th)	17.6 mg/m ²	30 (22,37)	35 mg/m ²	52 (42,60)
12–15	1.9 m ² (90th)	15.8 mg/m ²	27 (19,33)	32 mg/m ²	51 (41,59)
16+	1.7 m ² (10th)	17.6 mg/m ²	37 (27,46)	35 mg/m ²	54 (42,63)
16+	1.9 m ² (50th)	15.8 mg/m ²	35 (25,43)	32 mg/m ²	51 (40,60)
16+	2.1 m ² (90th)	14.3 mg/m ²	32 (23,40)	29 mg/m ²	49 (39,58)

* Dosing for COG study AREN0533, regimen DD4A.

** Percentiles are for patients in the age group and are approximate. The dose caps apply to patients < 55kg for AMD and < 1.3 m² for VCR resulting in lower cumulative dose with increasing size (see text).