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Patterns of chemotherapy-induced toxicities and outcome in children and adolescents with metastatic rhabdomyosarcoma: A report from the Children's Oncology Group

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Abstract

Background—We sought to determine whether adolescents with metastatic alveolar rhabdomyosarcoma (ARMS) or embryonal RMS (ERMS) had a different event-free survival (EFS) compared with younger patients, and to identify treatment-related factors (adverse events, AEs) that may be associated with differences in outcome.

Methods—The prevalence of AEs in adolescents older than 13 years was compared with that in patients less than or equal to 13 years of age (Fisher exact test) in patients enrolled onto ARST0431. EFS by age and histology was compared by log–rank test.

Results—Of 109 patients, 60 (55%) were older than 13 years; they were more likely to have nausea (17 vs. 4%, $P = 0.06$) and pain (20 vs. 6%, $P = 0.05$) compared with younger patients. Adolescents were less likely to complete therapy (63 vs. 76%) and more likely to have unplanned dose modifications outside of protocol guidelines (23 vs. 2.7%). The 3-year EFS was 26% (95% confidence interval [CI]: 15–38) for adolescents compared with 46% (95% CI: 32–60) for those

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less than or equal to 13 years (P = 0.011). Forty-two (59%) adolescents with ARMS had a 3-year EFS of 13% (95% CI: 2–23) compared with 30% (95% CI: 10–51) for those less than or equal to 13 years ($P = 0.032$). EFS was comparable between older and younger patients with ERMS (64 vs. 55%, $P = 0.53$).

Conclusions—Although there was a significant difference in EFS and protocol compliance by age, the differences in age-related toxicity are unlikely to account for this. Observed differences in pain and nausea by age could be real or be dependent on patient reporting of symptoms. Future studies in RMS should include patient-reported outcomes to better evaluate health-related quality of life.

Keywords

adolescent; chemotherapy; rhabdomyosarcoma; toxicity

1 | INTRODUCTION

Patients with metastatic rhabdomyosarcoma (RMS) account for 16% of all cases of RMS.[1–3] The 5-year progression-free survival of patients (age <21 years) with metastatic disease on Intergroup Rhabdomyosarcoma Study III was 27–30%.[1] A pooled analysis of patients with metastatic disease from both North American and European cooperative groups identified age younger than 1 year or greater than 10 years to be negatively correlated with event-free survival (EFS), with a relative risk of relapse or death of 1.6 (95% confidence interval [CI]: 1.4–1.9, $P < 0.0001$).[4] We previously demonstrated that adolescents with intermediate risk (nonmetastatic) RMS experience less hematological and more peripheral nervous system toxicity than younger patients.[5,6] In order to determine if the same trends exist in adolescents and young adults (AYAs, ages >13) with metastatic RMS, we sought to determine whether age-related differences in toxicity and disease-related outcome persisted in the context of modern therapy for metastatic RMS.

We used the recently completed Children's Oncology Group (COG) study, "Intensive Multi-Agent Therapy, Including Dose-Compressed Cycles of Ifosfamide/Etoposide (IE) and Vincristine/Doxorubicin/Cyclophosphamide (VDC) for Patients with High-Risk Rhabdomyosarcoma" (ARST0431) to complete this analysis.[7]

2 | METHODS

2.1 | Patients

We reviewed toxicity data for 109 patients on ARST0431; details of treatment and outcome have been published previously.[7] Patients were included in this study if they were less than 50 years of age and had metastatic rhabdomyosarcoma or ectomesenchymoma, good performance status, and no prior chemotherapy or radiation therapy. The treatment schema and chemotherapy dosing are shown in Figure S1 in Supplementary Materials. Twenty patients received irinotecan daily for 5 days for 2 weeks per course (VIx5×2) and 89 patients received irinotecan daily for 5 days for 1 week per course (VIx5×1). Criteria for stopping therapy included progressive disease, intolerable toxicity, refusal of further protocol therapy by patient/parent/guardian, completion of planned therapy, physician determination that it is

in patient's best interest, or diagnosis of a second malignant neoplasm. Prescribed dose modifications included delay of starting next cycle of therapy for low blood counts, dose reduction of cyclophosphamide by 25% for renal dysfunction (creatinine clearance < 10 ml/min/1.73 m^2), elimination of ifosfamide for severe renal dysfunction, dose reduction by 25% of vincristine and actinomycin for hyperbilirubinemia, delay or discontinuation of doxorubicin for cardiac toxicity, and delay of vincristine for peripheral neuropathy. For mucositis secondary to doxorubicin, the protocol suggested shortening infusion time from 48 to 24 hr, or reducing dose by 25% for persistent toxicity. Often, patients were noted to have dose modifications that fell outside these suggestions and are listed as "unplanned dose modifications." Of note, myeloid growth factor was required on study, but prophylactic antibiotics were not. Toxicity data that were grade 3 or higher were extracted from patient chart by data coordinators and documented as an adverse event that was either severe, life threatening, or causing death.

2.2 | Statistical considerations

Adverse events (AEs) as assessed by CTCAEv3.0 included toxicity of grade 3 or higher and were recorded.[8] For example, grade 3 pain is described as severe pain or pain or analgesics severely interfering with activities of daily living and grade 3 nausea is associated with inadequate oral caloric or fluid intake, or requiring IV fluids, tube feedings, or total parenteral nutrition for 24 hr or more. The rate of various AEs was compared between the age groups: younger patients (≤13 years of age) or adolescents (>13 years of age), separately for each reporting period (four reporting periods [protocol weeks 1–6, 7–19, 20–34, and 35–54]) using the Fisher exact test. We chose age 13 years as a cutoff to separate the population into those who are most likely to be pre- vs. post-pubertal.

EFS was defined as the time from study entry to the first occurrence of progression, relapse after response, or death from any cause. Patients who did not experience an event were censored at their last follow-up. EFS distributions were estimated using the Kaplan–Meier method[9] and were compared using the log–rank test.[10] Statistical significance was determined at the 0.05 level.

3 | RESULTS

3.1 | Patient demographics

The demographics of patients included in this analysis are summarized in Table 1. Seven (6%) patients were greater than 21 years of age. The younger patients who were less than or equal to 13 years had a median age of 5.14 years (range 0.45–12.27 years) and the adolescents older than 13 years had a median age of 16.17 years (range 13.3–29.9 years).

3.2 | Toxicity

Table 2 shows the association of individual toxicities (grade 3+) with age for each of the reporting periods. During the first reporting period (weeks 1–6), nausea/vomiting (17 vs. 4%, $P = 0.06$) and pain (20 vs. 6%, $P = 0.05$) were more common in adolescent than in younger patients. During the fourth reporting period (weeks 35–54), infection was less

prevalent in adolescents compared with younger patients (13 vs. 33%, $P = 0.02$). There were no other significant associations between toxicities and age.

All other toxicities were similar between the two age cohorts in the other reporting periods (RPs). A total of 34 patients did not complete RP4. Adolescents were less likely to complete therapy (≤13 years: 76%; >13 years: 63%) and more likely (in RP 4) to have unplanned dose modifications (outside of protocol guidelines) (23 vs. 2.7%). Most common reasons for failing to complete therapy included refusal (patient/parent) or physician determined not in best interest (≤13 years: 38%; >13 years: 70%) and disease progression (≤13 years: 38%; >13 years: 22%). Of the 65 patients who completed all therapy, there was no difference in the time required to complete therapy between the two groups (≤13 years: 63 ± 3.7 weeks vs. >13 years: 64.5 ± 8.8 weeks, $P = 0.64$). There were only two toxic deaths, both in RP3, one as a result of infection (16.8 years of age) and one as a result of concurrent cytomegalovirus infection and radiation pneumonitis (3.2 years).[11]

3.3 | Outcome

With a median follow-up of 7.4 years (range: 0.06–8.8 years) in surviving patients, the 3-year EFS and OS for all patients were 35% (95% CI: 26–44) and 56% (95% CI: 46–66), respectively. There was a statistically significant difference in EFS among the whole group (46% [32%, 61%], n = 49 for younger and 27% [15%, 38%], n = 60 for older; $P = 0.011$). EFS was similar among patients with ERMS: 55% (33%, 77%, n = 21) and 64% (39%, 89%, n = 15) for younger and older patients, respectively ($P = 0.53$). There was a significant difference in EFS among patients with ARMS: 30% [10.1%, 50.6%], n = 22 and 12.6% [2.3%, 22.9%], n = 42) for younger and older patients, respectively. ($P = 0.032$). Adolescents with ERMS had significantly superior EFS and OS compared with adolescents with ARMS ($P = 0.004$ and $P = 0.018$, respectively).

To explore the association of toxicities with EFS, a “landmark analysis” was conducted.[12] Adolescent patients included in the analysis were only those who were alive and failure-free at the end of Reporting Period 2 (weeks 7–19). A patient was considered to have had a particular toxicity if it occurred in either of the first two reporting periods. For example, a patient was considered to have had grade 3+ diarrhea if it occurred at any point during weeks 1–19. For this analysis, EFS was determined as the time from the end of reporting period 2 until disease progression or death. We could not find any association between toxicity experienced and EFS. Specifically, each individual grade 3+ toxicity reported on Table 2 was not associated with time to disease progression or death after a patient was treated for 19 weeks.

4 | DISCUSSION

Adolescents greater than 13 years of age with metastatic RMS have an inferior disease-related outcome and different patterns of chemotherapy-induced toxicity with increased pain and nausea when compared with younger children. Adolescents were less likely to complete protocol therapy and more likely to have unplanned dose modifications despite having fewer infections later in therapy. The retrospective nature of this review limits our ability to attribute an inferior outcome to the increased reporting of pain and nausea, which may or

may not have directly contributed to dose modification or protocol deviations. Furthermore, it is possible that patients or physicians chose not to continue therapy based on nonreportable toxicity (i.e., Grade 2 nausea or fatigue). With the lack of excessive hematological toxicity, infection, toxic death, or differences in time to complete protocol therapy, we were unable to demonstrate that measurable differences in toxicity would account for differences in survival outcomes. The analysis of outcome is further limited by the inadequate data collection and follow-up for patients who were removed from protocol therapy.

Adolescents were more likely to report nausea and pain compared to younger children, which raises the question of whether there is truly a difference in these symptoms by age, or whether age impacts patient-reporting of such subjectively experienced toxicities. Others, for example, have found that adolescents (15–17 years old) report worse health-related quality of life (HRQOL) than young adults (ages 18–25),[13] and the CTCAE may underestimate the prevalence of subjective symptoms by as much as 40%.[14] Interestingly, adolescents continued to report pain throughout their treatment course, with lowest pain being reported in the last reporting period. This may reflect decreased tumor burden and/or more successful pain management over time. For younger patients, pain was reported the lowest in the first reporting period and highest in the third.

Studies in RMS have so far used reporting by healthcare professionals in the medical chart to document toxicity. Patient reported outcomes and data on HRQOL among patients with RMS are limited to small studies of survivors of perineal or pelvic disease.[15,16] There have been no previous published reports prospectively assessing HRQOL or symptoms during therapy for RMS. Our findings underscore the need for rigorous patient-reported outcomes research in this population; less common completion of therapy, more common dose modifications, and more common complaints of distressing symptoms like pain and nausea may all contribute to poor adherence to medical recommendations and, ultimately, higher risk of recurrence. By measuring specific symptoms as well as generic HRQOL, supportive care interventions can be prioritized, and anticipatory counseling can be facilitated with the goal of improving compliance to protocol therapy.[17–19]

The impact on HRQOL with targeted therapies has been extensively studied in adults, for example, with renal cell carcinoma, due to the high frequency of disease, minimal change in EFS, numerous biological agents available, and chronicity of therapy.[20,21] In this population, patients with similar EFS reported improved QOL with temsirolimus compared with interferon therapy, rendering temsirolimus the drug of choice.[22] Likewise, Ruxolitnib was approved for treatment of myelodysplasia based on improvements in patient-reported pain compared with placebo.[23] It follows that appropriate symptom-control, due to tumor regression and supportive care intervention, is associated with improved HRQOL.

Future COG RMS clinical trials will strive to evaluate the role of biologically targeted therapies to improve outcome for patients with both intermediate- and high-risk disease.[24] Smaller differences in out-come may be offset by larger differences in HRQOL between standard and experimental arms. There are several instruments that can be used to assess HRQOL in the pediatric population, the most common being Pediatric Quality of Life

Inventory, PedsQL 4.0. Validity of the PedsQL 4.0 Generic Core Scales and Acute Cancer Module were established by known group comparisons and correlations with other measures of disease burden.[17,25] More recently, the PedsQL 4.0 Generic and Acute Cancer modules have been developed for young adults (18–25 years). These young adult-focused versions have been validated against established group comparisons and measure the same domains as the child and adolescent instruments.[17]

In summary, adolescents with metastatic ARMS reported pain and nausea more frequently than younger patients, but it remains unclear whether these differences in toxicity correlate with the higher dose modifications or reluctance to complete protocol therapy. In turn, these findings mayor may not correlate with poor disease-related survival. Thus, prospective evaluation of HRQOL of patients is required to help inform best treatment options for patients and has become a goal for future studies in RMS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AEs	adverse events
ARMS	aleveolar rhabdomyosarcoma
AYAs	adolescents and young adults
CI	confidence interval
COG	Children’s Oncology Group
EFS	event-free survival
ERMS	embryonal rhabdomyosarcoma
HRQOL	health-related qualityof life
IE	ifosfamide/etoposide
OS	overall survival
PedsQL	Pediatric Qualityof Life
QOL	qualityof life
RMS	rhabdomyosarcoma
RPs	reporting periods

VDC	vincristine/doxorubicin/cyclophosphamide
VIx5×1	irinotecan dailyfor 5 daysfor 1week per course
VIx5×2	irinotecan daily for 5 days for 2 weeks per course

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TABLE 1

Patient demographics

Variable	Age ≤13 years (%[a])	Age >13 years (%[a])	Total (%[b])
Sample size	49	60	109 (100)
Sex Male	27 (55)	33 (55)	60 (55)
Histology			
Alveolar	22 (45)	42 (70)	64 (59)
Embryonal	21 (43)	15 (25)	36 (33)
Other	6 (12)	3 (5)	9 (8)
Primary site			
Extremity	10 (20)	9 (15)	19 (17)
Gentinourinary	4 (8)	9 (15)	13 (12)
Head and neck	4 (8)	0	4 (4)
Parameningeal	6 (12)	5 (8)	11 (10)
Perineum/anus	2 (4)	9 (15)	11 (10)
Bladder/prostate	1 (2)	7 (12)	8 (7)
Intrathoracic	0 (0)	3 (5)	3 (3)
Retroperineum	7 (14)	7 (12)	14 (13)
Trunk	10 (20)	6 (10)	16 (15)
Other	5 (10)	5 (8)	10 (9)
Tumor size			
<5 cm	14 (29)	8 (13)	22 (20)
≥5 cm	35 (71)	52 (87)	87 (80)
Number of patients who completed each reporting period			
1 (weeks 1–6)	49 (100)	59 (98)	108 (99)
2 (weeks 7–19)	44 (90)	57 (95)	101 (93)
3 (weeks 20–34)	40 (82)	50 (83)	90 (83)
4 (weeks 35–54)	37 (76)	38 (63)	75 (69)

[a]Percentage within the age group.

[b]Percentage with respect to the entire sample.

TABLE 2

Association of grade 3+ toxicities and age by reporting period

Reporting period	Toxicity	≤13 years (%[a])	>13 years (%[a])
1 (weeks 1–6)		n = 49	n = 59[c]
	Diarrhea	7 (14.3)	12 (20.3)
	Mucositis	2 (4.1)	1 (1.7)
	Nausea/vomiting	2 (4.1)	10 (16.9)
	Infection	4 (8.2)	13 (22.0)
	Metabolic	6 (12.2)	8 (13.6)
	Pain[b]	3 (6.1)	12 (20.3)
	Hematology	2 (4.1)	3 (5.1)
	Peripheral nervous	0 (0)	0 (0)
	system		
2 (weeks 7–19)		n = 45	57
	Diarrhea	2 (4.4)	1 (1.8)
	Mucositis	8 (17.8)	6 (10.5)
	Nausea/vomiting	3 (6.7)	4 (7.0)
	Infection	23 (51.1)	28 (49.1)
	Metabolic	7 (15.6)	5 (8.8)
	Pain	4 (8.9)	9 (15.8)
	Hematology	2 (4.4)	1 (1.8)
	Peripheral nervous	1 (2.2)	6 (10.5)
	system		
3 (weeks 20–34)		n = 41	n = 51
	Diarrhea	9 (22.0)	9 (17.6)
	Mucositis	2 (4.9)	8 (15.7)
	Nausea/vomiting	3 (7.3)	5 (9.8)
	Infection	25 (61.0)	29 (56.9)
	Metabolic	8 (19.5)	7 (13.7)
	Pain	4 (9.8)	11 (21.6)
	Hematology	2 (4.9)	5 (9.8%)
	Peripheral nervous	1 (2.4)	6 (11.8)
	system		
4 (weeks 35–54)		n = 38	n = 43
	Diarrhea	5 (13.2)	4 (9.3)
	Mucositis	1 (2.6)	0 (0)
	Nausea/vomiting	4 (10.5)	3 (7.0)
	Infection[b]	16 (42.1)	8 (18.6)
	Metabolic	2 (5.3)	3 (7.0)

Reporting period	Toxicity	≤13 years (%[a])	>13 years (%[a])
	Pain	2 (5.3)	5 (11.6)
	Hematology	3 (7.9)	1 (2.3)
	Peripheral nervous system	1 (2.6)	3 (7.0)

[a]Percentage within the age group.

[b]Percentage statistically significant difference between the age group at the 0.05 level.

[c]Including 13 with age >18 years.