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Clinical characteristics and outcomes of adult alveolar rhabdomyosarcoma patients on first-line systemic therapies: A single-institution cohort

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Abstract

Background: Rhabdomyosarcomas are the most common soft tissue sarcoma in children, and pediatric alveolar rhabdomyosarcoma (ARMS) prognosis has improved based on cooperative studies. However, in adults, ARMS is significantly rarer, has poorer outcomes, and currently lacks optimal treatment strategies. **Objective:** This study aimed to evaluate the clinical outcome of an adult ARMS population with different front-line systemic chemotherapies and determine if any chemotherapy regimen is associated with improved survival. **Materials and methods:** This is a retrospective study of histologically confirmed fusion-positive ARMS patients over 18 years of age, who were treated at MD Anderson Cancer Center (MDACC) from 2004 to 2021 and received systemic chemotherapy. Descriptive clinical statistics were performed, including staging, front-line chemotherapy, multimodal therapy usage, response rates, and survival analyses. **Results:** 49 ARMS patients who received upfront chemotherapy were identified. Locoregional treatments included radiotherapy (RT) alone (29%, *n* = 14), surgery alone (10%, *n* = 5), or both (45%, *n* = 22). Median overall survival (OS) for the entire cohort was 3.6 years, and the overall response rate to systemic therapy was 89%. No chemotherapy regimen showed OS benefit, specifically analyzing the pediatric-based vincristine, actinomycin-D, cyclophosphamide (VAC) or adult-based vincristine, doxorubicin, ifosfamide (VDI) regimens, even when controlled for other clinical risk factors. **Conclusion:** In this single-center contemporary series, adult ARMS patient outcomes remain poor. There was no statistically significant OS difference in patients who did or did not receive adult or pediatric based ARMS regimens, although a high overall response rate to chemotherapy was seen across the entire cohort. Based on these observations, further randomized prospective studies are necessary to delineate which frontline chemotherapy regimen is most beneficial in this rare adult cancer.

Keywords

Sarcoma, soft tissue sarcoma, alveolar rhabdomyosarcoma, chemotherapy

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Introduction

Although rare, rhabdomyosarcoma (RMS) is one of the most common soft-tissue sarcoma (STS) in children, representing ~50% of STS cases.[1] However, not only are STS proportionally less common in adults, RMS represents just 3% of new STS diagnoses.[2]

Multimodal therapy with surgery, chemotherapy, and radiotherapy (RT) has become the standard of care for pediatric rhabdomyosarcoma patients, providing cure rates can exceed 70% for those presenting with localized disease.[3–5] Although several retrospective studies have suggested a benefit using this multimodal approach in adults, systematic trials and uniform multimodal treatment still need to be fully developed, given its rarity in adults.[6] Adult RMS patients consistently have worse outcomes than children, with 5-year OS ranging from 21%–53%.[2] Additionally, no specific trial has established a preferred front-line regimen in adults. Older patients rarely participate in pediatric RMS protocol trials. Yet, pediatric protocol-based chemotherapy treatments are commonly extrapolated for use in these patients, and retrospective analyses have suggested their use may improve outcomes.[7]

The alveolar rhabdomyosarcoma (ARMS) subtype represents roughly 22%–33% of RMS in adults,[8,9] and most of these patients will harbor PAX-FOXO1 fusion translocations.[1,10] As in pediatrics, adult ARMS patients have a worse prognosis than embryonal rhabdomyosarcoma, but have a similarly poor prognosis as pleomorphic rhabdomyosarcoma, the most common subtype of rhabdomyosarcoma in adults.[7,11] From the IRSG and Children's Oncology Group trials in ARMS pediatric patients, the standard first-line chemotherapy regimen remains vincristine, actinomycin-D, and cyclophosphamide (VAC).[3] However, it is unclear whether this is the most effective regimen for ARMS in adults.

Prior studies have suggested that ifosfamide has higher response rates than cyclophosphamide in STS.[12] Still, there have been no randomized controlled trials to establish the superiority of one over another.[13] In pediatric RMS, VAI (vincristine, actinomycin D, ifosfamide) was not found to be superior to VAC.[3] Although the addition of doxorubicin to actinomycin-D containing regimens has not shown significant benefit in pediatric RMS,[14] in adults, doxorubicin is effective in many soft-tissue sarcomas[15] and is often used in adult rhabdomyosarcoma chemotherapy regimens.[16,17] Given the different clinical outcomes in adult RMS compared to pediatrics, possibly related to multiple factors including differing tumor biology, associated differences in risk factors, and chemotherapy tolerance, the optimal treatment regimen in the adult population remains unknown. Without specific treatment guidelines, best practice and expert opinion guidelines have been used to treat these patients. We therefore retrospectively analyzed adults treated for ARMS in our institution to determine whether different first-line chemotherapy regimens lead to improved clinical outcomes.

Methods

Patient selection

Institutional approval through the institutional review board (IRB) was obtained before initiating the study. A retrospective chart review of the University of Texas M.D. Anderson Cancer Center (MDACC) patient registry was performed to identify all patients ≥18 years of age diagnosed with ARMS (by IHC markers and/or PAX-FOXO1 fusion testing confirmation) who were in the clinical registry and seen by a medical oncology provider from 2004 to 2021. Patients whose tumors were confirmed to lack the PAX-FOXO1 fusion were excluded. Patients must have received at least one line of chemotherapy to be included. Patients did not have to have first-line treatment at MDACC to be included; many patients referred to our center had prior treatment(s). Patient demographic features, including age and race were collected.

These patients' clinical, pathological, staging and follow-up data were collected. This included Children's Oncology Group (COG) risk group according to COG guidelines, primary disease site location, length of follow-up, types of front-line chemotherapy regimens used, number of frontline cycles of chemotherapy administered, use of radiation therapy or surgery, progression-free survival (PFS), disease-free survival (DFS), and overall survival (OS). OS was calculated from the date of diagnosis, and PFS was calculated from the time chemotherapy was initiated. Treatment response was confirmed by review using RECIST 1.1 criteria, and best response during first-line chemotherapy was recorded. Since the primary imaging methods were inconsistent and sometimes unavailable for review, the best response was assessed by our clinicians.

Histologic review

Histologic confirmation of ARMS by sarcoma pathologists at MDACC was required for all cases evaluated for this retrospective study using standard WHO criteria. Molecular diagnostics included fluorescence in-situ hybridization (FISH), real-time polymerase chain reaction (RT-PCR), and/or fusion analysis by next-generation sequencing (NGS) panels. FISH for FOXO1 at 13q14 was the most common method for diagnostic confirmation.

Statistics

The primary endpoints in this study were OS and DFS for patients achieving remission after first-line therapy. Response rates were determined based on RECIST 1.1. The Kaplan-

Meier method was used to estimate survival outcomes, and the log-rank test was used to test for the significance of differences between curves. Multivariable analyses were conducted using the Cox proportional hazards model. Analyses were generated with GraphPad Prism version 9, and statistical significance was assessed with p-values <0.05. Chi-square analysis was also performed with GraphPad Prism.

Results

Patient demographics

The registry query resulted in 53 ARMS patients meeting the search criteria. However, four patients lacked appropriate histologic confirmation. Of the 49 remaining patients with pathologically confirmed ARMS, 29 had PAX-FOXO1-based fusions confirmed, while the other 20 patients were diagnosed by typical morphologic assessment and immunohistochemistry. The median follow-up time from initiation of first-line systemic therapy for patients was 2.29 years (range 0.16–12.6 years). Other demographic data are shown in Table 1. The median age of patients was 32 years (range 18–67 years), with the sex distribution not significantly different. The most common primary tumor site was the parameningeal space (59%; n = 29), and patients were either classified as intermediate (67%) or high COG clinical risk[18,19] (33%). Stratified by Intergroup Rhabdomyosarcoma Study Group (IRSG) clinical group,[20] patients were IIIa (39%), IIIb (20%), or IV (33%). At diagnosis, 20 patients (41%) had evidence of nodal involvement and 16 patients (33%) had distant metastatic disease.

Table 1. Baseline clinical characteristics of adult ARMS patients.

Clinical parameters	Total patients (n = 49) (%)
Age	32 (19-67)
Sex	26 M 23 F
Race	
White	26 (53)
Asian	7 (14)
Hispanic	10 (20)
Black	6 (12)
Primary site	
Paramengingeal	29 (59)
Head and neck	6 (12)
Genitourinary	4 (8)
Bladder/prostate	1 (2)
Extremities	5 (10)
Perirectal	3 (6)
Other	1 (2)
Clinical risk	
Intermediate	33 (67)
High	16 (33)
Clinical group	
I - II	3 (6)
IIIa	19 (39)
IIIb	10 (20)
IV	16 (33)
Unknown	1 (2)
Clinical stage	
1	1 (2)
2	8 (16)
3	23 (47)
4	16 (33)
Unknown	1 (2)
Distant disease	
No node/distant	13 (27)
Nodal only	20 (41)
Nodal + metastases	35 (71)
Distant metastases	16 (33)

Front-line systemic therapy characteristics

As part of the initial management, all patients in our cohort received chemotherapy. A majority of patients received multimodal therapy during their upfront treatment, with RT alone (29%, n = 14), surgery alone (10%, n = 5), or both (45%, n = 22). Of those patients who underwent upfront RT, 36% (13/36) received it in the neoadjuvant setting, 42% (15/36) in the adjuvant setting, and 25% (8/36) palliatively for metastatic disease. Patients who received RT as part of initial management was associated with improved survival, although this was confounded by a higher proportion of these patients having localized disease (28/36 patients) than those who did not receive radiation (5/8 patients) (p = .01) (Supplemental Figure 1). The median dose of radiation to the primary tumor for localized disease patients was 60 Gy, and 50.4 Gy in the metastatic setting. Of the 22 patients who underwent surgery as part of their frontline multimodal treatment, 15 had localized disease at initial presentation, and 11/15 (27%) of these patients underwent complete resection with only 36% (4/11) achieving negative margins.

A total of 27 patients received first-line chemotherapy at an outside facility, 19 at MDACC, and 3 at both. Of the 49 patients, 4 received chemotherapy in the adjuvant setting, while the rest received chemotherapy in the neoadjuvant or unresectable/metastatic setting. The different first-line chemotherapy regimens administered are shown in Table 2 and consisted of several diverse regimens mostly centered around vincristine, actinomycin-D and cyclophosphamide (VAC) or vincristine, doxorubicin, and ifosfamide (VDI) backbones. The median number of chemotherapy cycles was 10 (range 1–20), and a majority included initial administration of three drug regimens such as VAC or VDI. Many patients also received secondary chemotherapeutics in the first-line setting such as ifosfamide, etoposide (IE) or vincristine, irinotecan, and temozolomide (VIT). We were interested in patients who received any VDI-containing regimen as part of initial

Table 2. List of first-line chemotherapy regimens given to ARMS patients.

VAC containing	No. patients
VAC	6
VAC-I-IT	1
VAC-CI-IE-VEC	1
VAC-VIT	1
VDC containing	
VDC-IE	4
VDC-VIT	1
VDC	1
VDC-other	3
VDI	
VDI	9
VDI-IT	1
VDI-IE	1
VDI-IE-other	3
VDI-other	4
Protocol based	
ARST0431	3
ARST0531	3
Other	3
Other	
Lobaplatin + fluorouracil	1
Cisplatin + etoposide	1
VEC	1
MAID	1
ADI	1

VAC: vincristine, actinomycin-D, cyclophosphamide; VDC: vincristine, doxorubicin, cyclophosphamide; VDI: vincristine, doxorubicin, ifosfamide; VEC: vincristine, epirubicin, cyclophosphamide; MAID: mesna, doxorubicin, ifosfamide, dacarbazine; ADI: bevacizumab, doxorubicin, ifosfamide; IE: ifosfamide, etoposide; IT: irinotecan, temozolomide; VIT: vincristine, irinotecan, temozolomide; CI: carboplatin, irinotecan; VAC-I-IT: VAC – ifosfamide with radiotherapy – IT; ARST0531: VAC or VAC + VI; ARST0431: vincristine, irinotecan - VDC - IE - VAC.

Table 3. Clinical characteristics patients who received VDI or non-VDI first-line chemotherapy regimen.

Clinical parameter	VDI (n = 18) (%)	Non-VDI (n = 31) (%)
Age (median)	35	34.8
Sex	6 male 12 female	20 male 11 female
Race		
White	8 (44)	18 (58)
Asian	2 (11)	5 (16)
Hispanic	5 (28)	5 (16)
Black	3 (17)	3 (10)
Primary site		
Parameningeal	13 (72)	16 (52)
Head and neck	2 (10)	4 (13)
Genitourinary	1 (6)	3 (10)
Bladder/prostate	1 (6)	0 (0)
Extremities	1 (6)	4 (13)
Perirectal	0 (0)	3 (10)
Other	0 (0)	1 (3)
Clinical risk		
Intermediate	12 (67)	20 (65)
High	6 (33)	11 (35)
Clinical group		
I - II	1 (6)	2 (7)
IIIa	8 (44)	11 (35)
IIIb	4 (22)	6 (20)
IV	5 (28)	11 (35)
Unknown	0	1 (3)
Clinical stage		
1	0 (0)	1 (3)
2	3 (17)	5 (16)
3	10 (56)	13 (42)
4	5 (28)	11 (36)
Not evaluable	0 (0)	1 (3)
Distant disease		
No nodal/distant	4 (22)	9 (29)
Nodal only	9 (50)	11 (35)
Distant metastasis	5 (28)	11 (35)

management, given its use in other adult rhabdomyosarcoma subtypes.[17] Only a minority of the study population (18 patients) received VDI, and the non-VDI chemotherapy regimens were heterogeneous (Table 2). Most non-VDI patients received VAC or VAC containing regimens (Table 2). There was no significant association between clinical factors such as clinical group, stage, or risk between VDI and non-VDI patients (Table 3).

Regarding response assessment, 28 (62%) of 45 patients had evaluable disease (4 patients received adjuvant chemotherapy), while 17 (35%) of 45 patients did not have evaluable disease due to lack of access of baseline imaging data. A total of 25 of the 28 evaluable disease patients responded to first-line treatment (89%). In terms of the maximal response noted to first-line chemotherapy, 12 (43%) patients' tumors showed a complete remission (CR) and 13 (46%) with a partial response (PR) to therapy by RECIST criteria. Chemotherapy led to stable disease as the best response in two patients, while treatment failure was noted with only one patient who had progression on chemotherapy. Of these 28 evaluable patients, 7 discontinued first-line systemic treatment due to disease progression, 5 due to toxicity (Supplemental Table 1), 1 due to loss of insurance coverage, and the remaining 15 due to completion of intended treatment (Table 4).

Survival outcomes of different chemotherapy regimens

The median overall survival for the entire patient cohort was 3.56 years (range 0.17–12.7 years), with a median follow-up time of 2.27 years (Figure 1A). Patients with localized disease

Table 4. Response rates of patients for different first-line chemotherapy regimens.

Chemotherapy regimen	No. patients	No. evaluable patients	NA	PD	SD	PR	CR
VAC-based regimen	15	5	8			1 (20%)	4 (80%)
VDI-based regimen	18	13	5	1 (8%)	2 (15.4%)	7 (54%)	3 (23%)
VDC-based regimen	8	6	2			2 (33%)	4 (67%)
VDC + VAC based regimen	3	2	1			2 (100%)	
Other regimen	5	2	3			1 (50%)	1 (50%)

NA: not analyzable; PD: progressive disease; SD: stable disease; PR: partial response; CR: complete response; VAC: vincristine, actinomycin-D, cyclophosphamide; VDI: vincristine, doxorubicin, ifosfamide; VDC: vincristine, doxorubicin, cyclophosphamide.

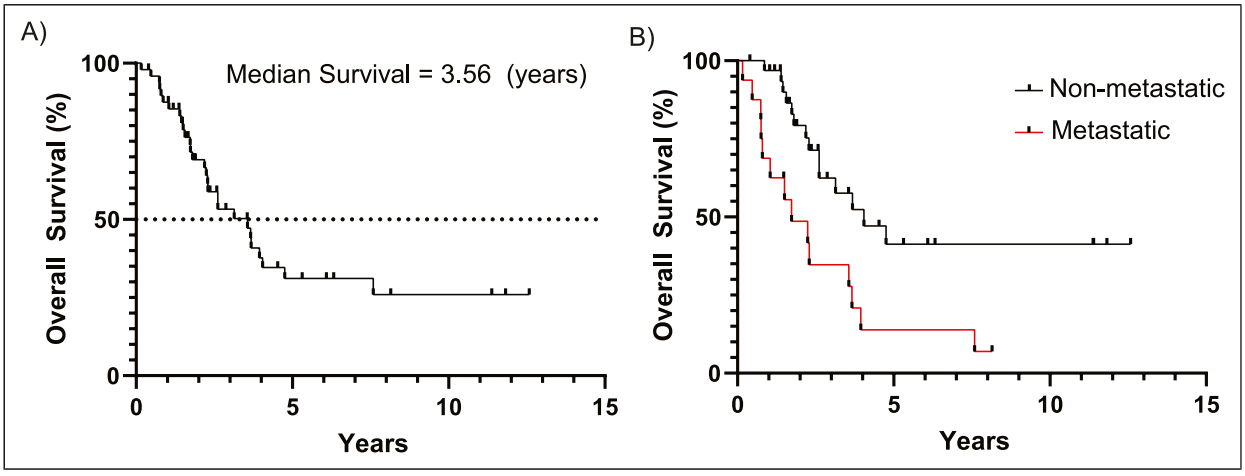

Figure 1. Overall survival of the adult ARMS patient cohort (A) Overall survival of all 49 adult ARMS patients, with median survival of 3.56 years. (B) Overall survival of patients with (n = 16) or without (n = 33) metastatic disease at presentation.

at diagnosis lived longer than those with metastatic disease; median OS of 4.05 years (range 0.4–12.7 years) versus 1.73 years (range 0.16–7.7 years) respectively (Figure 1B) (p = .0035). Expectedly, survival was worse in the higher clinical stage groups, with the median OS of groups 1-2, group 3, and group 4 of 4.8 years, 3.7 years, and 2.2 years, respectively (Supplemental Figure 2). Comparing all patients who received doxorubicin-based regimens versus non-doxorubicin, there was no statistically significant difference in overall survival of 2.3 years versus 4.0 years respectively (p = .36, HR 1.48, 95% CI 0.68–3.19) (Figure 2).

More specifically, we assessed whether patients receiving VDI had different overall survival than non-VDI regimens. There was no significant improvement with VDI compared to non-VDI treatment, with a median OS of 1.8 years versus 3.9 years (p = .28, HR 1.56, 95% CI 0.67–3.6) (Figure 3A). Additionally, we examined whether VDI improved overall survival in patients with localized disease. We found no significant difference in VDI or non-VDI regimens in localized ARMS (2.3 vs 4.8 years, HR 1.8, 95% CI 0.58–5.9) or metastatic ARMS (1.7 vs 2.2 years, HR 1.7, 95% CI 0.45–6.5) (Supplemental Figure 3). In terms of best response rates in VDI versus non-VDI patients, there was no

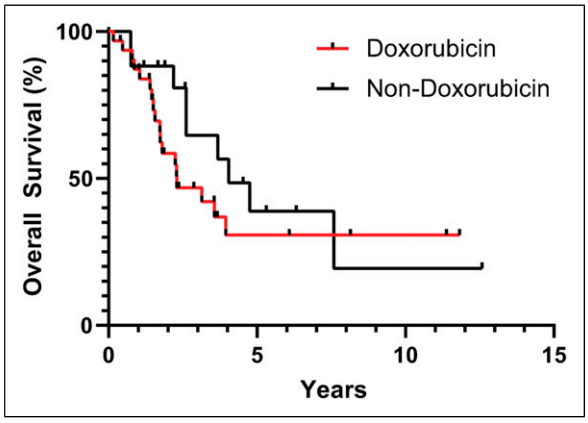

Figure 2. Overall survival of adult ARMS patients based on doxorubicin containing chemotherapy regimens Overall survival of patients who received doxorubicin (n = 32) or no doxorubicin (n = 17) within their upfront chemotherapy regimen.

significant difference in the CR and PR rate of maximal response either (p = .14). Regarding the use of VAC-based regimens, median OS was also not significantly different between patients who received VAC (3.6 years) and

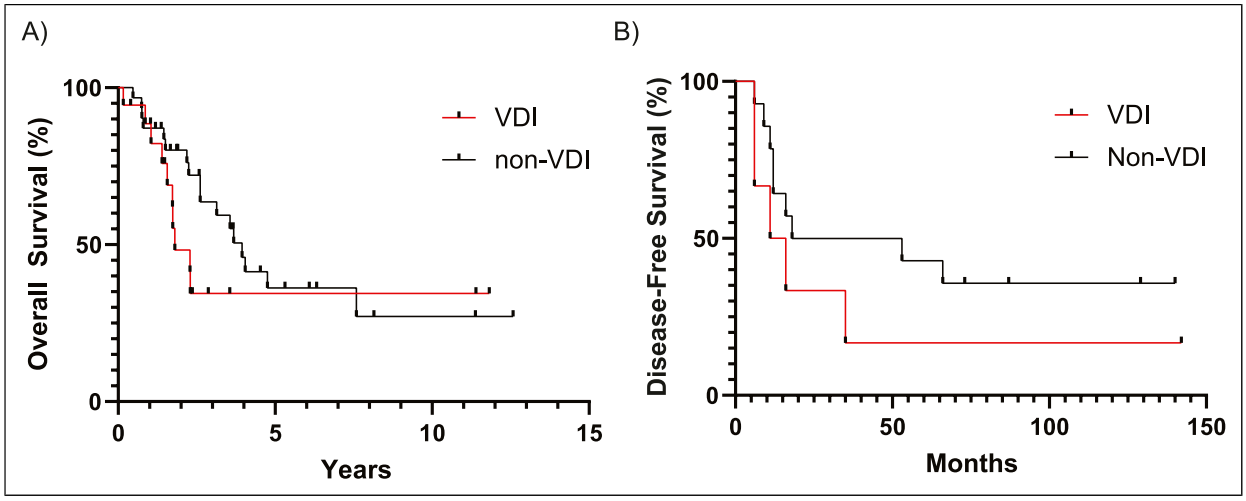

Figure 3. VDI vs non-VDI regimens and overall survival of ARMS patients (A) Overall survival of patients who received upfront VDI (n = 18) or non-VDI (n = 31) chemotherapy upfront. (B) Duration of response in patients who achieved a CR with VDI chemotherapy (n = 6) or non-VDI chemotherapy (n = 14).

non-VAC (3.1 years) (p = .95, HR 1.03, 95% CI 0.47–2.23) (Supplemental Figure 4A). Similar to our VDI analyses, we also did not see a significant difference in survival in patients with localized disease receiving VAC (4.0 years) compared to non-VAC (3.1 years) (p = .61, HR 1.29, 95% CI 0.46 – 3.63) (Supplemental Figure 4B).

Durability of response in VDI and non-VDI upfront regimens

We next compared whether specific regimens led to more prolonged response durability in patients who achieved a complete response after upfront therapy. In patients receiving VDI versus non-VDI who achieved a CR during upfront therapy, the median DFS was 11 months (n = 7) versus 53 months (n = 13) (p = .09) (Figure 3B). As the non-VDI chemotherapy regimens were heterogeneous, we next compared doxorubicin versus non-doxorubicin-containing regimens against VDI. Again, there were no significant differences in overall survival between the 3 groups (Supplemental Figure 5). As pediatric ARMS is treated with prolonged chemotherapy (up to 14 cycles),[4] we hypothesized that the number of upfront chemotherapy cycles might impact outcomes. However, there was no significant difference between the number of frontline cycles completed between VDI and non-VDI regimens either (8.52 vs 9.48 cycles, p = .49).

Discussion

Alveolar rhabdomyosarcoma is an extremely rare cancer in adults, with unfortunately poor outcomes and no standardized treatment regimens developed for these patients. Although great strides have been made in treating rhabdomyosarcoma in children from the Intergroup Rhabdomyosarcoma Studies,[3] the alveolar subtype, particularly the 80% that contain PAX-FOXO1 fusions, remains a poor prognostic factor.[21,22] 5-year OS from the time of diagnosis ranges from 64%–87% in localized pediatric ARMS cases. But after relapse, the 5-year survival from the time of recurrence is only 5%.[23] After metastatic disease, FOXO1 fusion status has been shown to be the most important prognostic factor in pediatric RMS.

Here we report the outcomes of a large cohort of 49 adult ARMS patients from a single institution. The overall survival of this cohort is similar to past adult ARMS studies,[7,9,24] with a median overall OS of 3.56 years and an average age at diagnosis of 34.6 years old. Most patients had primary disease originating in the parameningeal space, and about a third had metastatic disease at presentation. Therefore, it is expected that only a minority of patients received multimodal therapy with chemotherapy, RT, and surgery in their upfront treatment. Overall response rates with chemotherapy in our cohort were high at 89%, with 43% of these patients achieving a complete response with therapy, which is consistent with prior data. Expectedly, patients with worse clinical stage and metastases at presentation had worse survival.

In our institution, doxorubicin-based combinations have been favored for adult sarcoma patients. In particular, our institution has often used VDI as our induction chemotherapy regimen for ARMS patients, as it has been thought that doxorubicin and ifosfamide are two of the most active agents in adults, which may improve the odds of successful subsequent local therapy (either RT or surgery).[17,25,26] For instance, in Ewing sarcoma, adults have worse outcomes than children using pediatric regimens, and VDI has been shown to have equivalent outcomes to historic adult

controls treated with the 5-drug pediatric regimen.[27] Adult patients with perceived chronic kidney disease or older age received a modified version of our induction therapy with vincristine, doxorubicin, and cyclophosphamide (VDC).

Interestingly, our results did not show an improved OS with doxorubicin-containing regimens, nor VDI in adult ARMS patients. The role of doxorubicin therapy remains controversial in pediatric rhabdomyosarcoma, with prior trials not demonstrating superiority of doxorubicin over actinomycin-D in multi-agent regimens.[28,29] Also, the addition of doxorubicin to actinomycin-D regimens in localized ARMS patients has not been shown to improve clinical outcomes.[14] Given the evolving definitions of risk groups and complexities of the chemotherapy regimens compared in these previous trials, it makes it difficult to ascertain directly the impact of doxorubicin in the ARMS population without a prospective trial directly comparing it to another chemotherapeutic agent.[30] We speculate that the highly chemo-sensitive nature of ARMS limits our ability to detect a regimen-specific difference in first-line overall response rates and survival. Prior studies of rhabdomyosarcoma have reported a positive impact of pediatric-based protocols in adult ARMS.[11] As pediatric ARMS regimens are up to 14 cycles of treatment, the chemotherapy regimen best tolerated in adults is preferable in this specific sarcoma subtype, although this remains to be determined prospectively.

The main limitations of this study include the retrospective design and heterogeneity in treatment approaches to adult ARMS patients in the frontline setting. Chemotherapy regimens included VAC-based protocols as well as VDI, and when subdivided by regimen, there were limited numbers of patients for each analyses making it challenging to detect benefit of one chemotherapy drug compared to another. Additionally, during upfront therapy, various secondary chemotherapies were given either due to toxicities encountered from initial chemotherapeutics or per protocol design, as well as the different number of chemotherapy cycles administered from each regimen. There were also differing number of cycles of secondary chemotherapeutics given in the front-line. This heterogeneity, in addition to the small sample size for each regimen, makes it challenging to correlate our observed outcomes with a specific chemotherapy regimen, let alone individual chemotherapies within a regimen, in addition to the retrospective nature of this analysis and the inherit biases and limitations with this type of study such as patient selection.

Given the assortment of treatment modifications noted in this study, the lack of a cohesive treatment approach for adult patients with alveolar rhabdomyosarcoma, and the rarity of this disease, it is imperative for adult sarcoma medical oncologists to develop a more unified approach to treatment similar to our pediatric oncology colleagues. Through existing cooperative groups such as the National Comprehensive Cancer Network (NCCN) or NCI Experimental Therapeutics Clinical Trials Network (ETCTN), there is an urgent need to form consensus recommendations for adult rhabdomyosarcoma, including ARMS, based on best available data to develop prospective studies. These measures should take into account factors such as clinical characteristics (i.e. age, performance status, organ function) that are specific to adults, molecular factors (i.e., fusion status), and application of new and emerging technologies (i.e., such as the use of circulating tumor DNA). Collectively, these efforts could provide a more uniform approach to the treatment of adult rhabdomyosarcoma with the goal of improving outcomes and ensuring safety for these patients.

Conclusion

In this study, there was a non-statistically significant trend towards improved OS for ARMS patients treated with non-doxorubicin or non-VDI regimens, but there was no difference in DFS in those patients who achieved CR. However, given the abovementioned heterogeneity, this study was not sufficiently powered to detect whether one chemotherapy regimen was inferior to another. A prospective trial specifically enrolling an adult ARMS population comparing specific doxorubicin/VDI-based and current pediatric VAC based regimens would be needed to answer this question, with this and other retrospective studies serving as benchmarks for clinical outcomes. Given the rarity of this disease in adults, a multi-institute or multinational cooperative study is likely necessary to directly address this question.

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Author contributions

Conception and design: MSN., APC.; collection and/or assembly of data: MSN, JAL, MAZ, RR, JAL, DMA, NS, VR, AJL, RSB, SRP, APC Data analysis and interpretation: MSN, EFN, APC, Manuscript first draft writing: MSN, JAL, AJB, JAL, DMA, NS, EFN, CLR, AJL, BAG, DJH, APC; Final approval of manuscript: all authors.

Declaration of conflicting interests

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Ethical statement

Ethical approval

(Include full name of committee approving the research and if available mention reference number of that approval): MD Anderson Cancer Center does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from patients for their anonymised information to be published (DR09-025).

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Data availability statement

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to the use of patient clinical data.

Supplemental Material

Supplemental material for this article is available online.

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