Localized Adult Ewing Sarcoma: Favorable Outcomes with Alternating Vincristine, Doxorubicin, Cyclophosphamide, and Ifosfamide, Etoposide (VDC/IE)-Based Multimodality Therapy

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Disclosures of potential conflicts of interest may be found at the end of this article.

Abstract

Background. In children with localized Ewing sarcoma (ES), addition of ifosfamide and etoposide to cyclophosphamide, doxorubicin, and vincristine (VDC/IE) improved 5-year overall survival (OS) to 70%–80%. Prior to delivery of VDC/IE in adults, 5-year OS was <50%. We reviewed our institutional outcomes for adults with ES who received VDC/IE-based treatment.

Materials and Methods. Between 1997–2013, 67 adults with localized ES were treated with curative intent. Local recurrence-free survival (LRFS), progression-free survival (PFS), and OS were determined using Kaplan-Meier method; comparisons were assessed with log-rank. Proportional hazard models were used to determine predictive factors.

Results. All patients received VDC/IE (median 14 cycles.) Local therapy was surgery for 33, radiation therapy for 17, or both for 17. Median follow-up for living patients was 5.2 years. Six patients had disease progression on therapy. Site of first failure was local for three, local and distant for two, and distant for ten. Five-year LRFS was 91%; 5-year LRFS was 96% for nonpelvic disease and 64% for pelvic disease ($p = .003$). Five-year PFS was 66%, and 5-year OS was 79%. On multivariate analysis, pelvic site had a 3.3 times increased risk of progression ($p = .01$).

Conclusion. Survival for adults with localized ES treated with VDC/IE-based multimodality therapy appears to be better than historical data and similar to excellent outcomes in children. Pelvic site of disease remains a predictor of worse outcome. Given the paucity of literature for adult ES, these data help validate VDC/IE-based therapy as an appropriate treatment approach for this rare disease in adults. *The Oncologist* 2017;22:1265–1270

Implications for Practice: Ewing sarcoma (ES) is rare in adults. Treatment approaches for adults have been extrapolated from the pediatric experience, and there is a sense that adults fare less well than children. We reviewed treatment outcomes in adults with localized ES treated with cyclophosphamide, doxorubicin, and vincristine in alternation with ifosfamide and etoposide (VDC/IE) as part of multimodality therapy. Survival outcomes appear to be better than historical data for adults and similar to the excellent outcomes for children. These data help validate VDC/IE-based therapy as an appropriate treatment approach for this rare disease in adults.

Introduction

Although typically considered a pediatric disease, about 30% of Ewing sarcoma (ES) cases arise in adults [1]. Current standard treatment for localized ES is a multimodality approach, combining chemotherapy and local therapy consisting of surgery and/or radiation therapy (RT) [2–8].

Advances in chemotherapy regimens for ES have improved survival dramatically over the past 40 years. In the 1970s, addition of doxorubicin to vincristine, actinomycin D, and cyclophosphamide improved 5-year overall survival (OS) from 28% to 65% for localized disease [2]. In 2003, Grier showed the addition of ifosfamide and etoposide, alternating with cyclophosphamide, doxorubicin, and vincristine (VDC/IE), further improved survival [4]. Most recently, VDC/IE given every 2 weeks as opposed to every 3 weeks has increased 5-year OS to 83% [6]. These landmark trials were conducted primarily in pediatric populations, and although patients of any age [2], up to age 30 [4], or up to age 50 [6], were eligible for participation, numbers of patients included

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over age 18 were small, with median age enrolled being 12–13.

Despite substantial high-quality data on localized ES, the majority of it is derived from the pediatric age group; data evaluating outcomes in adults are scarce. There are no randomized trials that specifically address treatment in adults; thus, standard treatment is extrapolated from literature derived from a younger patient population. It is not clear whether outcomes are different in adults than children, as nearly all reviews pertaining to adults have small patient populations or also included patients less than 18 [9–16]. Furthermore, the majority of reviews were performed prior to the VDC/IE era. Accordingly, we evaluated outcomes for adults with localized ES treated exclusively with VDC/IE in combination with local therapy at our institutions.

MATERIALS AND METHODS

Patients

We conducted an Institutional Review Board-approved review of all adult patients ($\geq$18 years old) with newly diagnosed localized ES treated at Dana-Farber Cancer Institute/Brigham and Women's Hospital and Massachusetts General Hospital in Boston, Massachusetts, between 1997 and 2013. Inclusion criteria were treatment with VDC-IE-based multimodality therapy, delivery of at least one treatment modality at our institutions, and availability of complete treatment information. For patients diagnosed at outside hospitals, pathology review was performed to confirm a diagnosis of ES. Patients with a prior diagnosis of cancer were excluded. The resulting cohort was composed of 67 patients. We collected patient, disease, treatment, recurrence, and survival characteristics through medical record review.

Treatment

Patients were treated with alternating VDC-IE chemotherapy. Chemotherapy doses were administered as follows: vincristine 2 mg/m^2 (capped at 2 mg) on day 1, doxorubicin 37.5 mg/m^2 on days 1 and 2, cyclophosphamide 600 mg/m^2 on days 1 and 2, ifosfamide 1,800 mg/m^2 on days 1–5, and etoposide 100 mg/m^2 on days 1–5. Each cycle of chemotherapy was supported by filgrastim. Doxorubicin was omitted after achieving a cumulative dose of 350 mg/m^2. At the beginning of the study period, patients were treated in 3-week intervals for 14–17 cycles [4]. Following publication of the randomized trial showing superiority of dose dense treatment with 2-week intervals [6], patients were considered for 14 cycles using 2-week intervals with a schedule reduction to 3-week intervals based on tolerance.

Patients were evaluated for local therapy at about week 12. Surgery was the preferred local modality unless it was judged to be associated with significant morbidity, in which case RT was recommended. RT doses were 55.8 Gy for gross disease and 50.4 Gy for resected disease with positive margins. RT technique consisted of three-dimensional conformal therapy or intensity modulated RT.

Outcomes

Local recurrence-free survival (LRFS) was defined from date of diagnosis to localized recurrence as a first site of recurrence or death. Patients were censored at the time of regional or distant recurrence (DR), and those without a recurrence were censored at date of last assessment. Progression-free survival (PFS) was defined from date of diagnosis to first reported event (recurrence, progression, or death). Patients without an event were censored at date of last assessment. OS was defined from date of diagnosis to death or date last known alive.

Statistical Analysis

Descriptive statistics were used to report patient characteristics. Radiographic response to chemotherapy prior to local therapy was defined for extra-osseous tumors following Response Evaluation Criteria In Solid Tumors 1.1 guidelines as complete response, partial response, or stable disease [17]. LRFS, PFS, and OS were calculated using the Kaplan-Meier method. A log-rank test was used to identify disease characteristics associated with time to event distributions. Step-down proportional hazard models were constructed to identify factors associated with PFS and OS. STATA v. 13 (StataCorp, College Station, Texas, http://www.stata.com/company/) was used for all analyses.

RESULTS

Patient Characteristics

Our cohort included 67 patients with localized ES. Patient characteristics are shown in Table 1. Median age at diagnosis was 28 years (range, 19–69); 13 (19%) patients were $\geq$40 years. Sixty percent of patients were male. Median follow-up for patients still alive was 5.2 years (range, 0.8–15.6). Primary tumor locations included extremity (29), pelvis (12), and other (26). Other sites included superficial and deep trunk (14), spine (5), central nervous system (4), and head and neck (3). Primary tumor tissue type was extraosseous for 31 and osseous for 36. Median age for osseous ES was 25 years (range, 19–51), and median age for extraosseous was 33 (range, 21–69). Median tumor size was 7.7 cm (range, 1.3–28.3).

Treatment

All patients received VDC/IE. The median number of definitive-intent chemotherapy cycles delivered was 14 (range, 1–17); the number of patients who received <12 cycles was 11 (16%), 12–13 cycles was 16 (24%), 14 cycles was 28 (42%), and 15–17 cycles was 12 (18%). The median number of cycles delivered for those <40 years old was 14 (range, 2–17) and for those $\geq$40 was 13 (range, 1–15). Thirty-one (46%) patients were treated with intended 2-week interval cycles. Forty-seven patients (71%) received initial induction chemotherapy. Twenty patients (29%) did not receive chemotherapy prior to local therapy. Of these 20 patients, 19 initiated treatment with local therapy (18 surgery and 1 concurrent chemotherapy and RT) because a diagnosis of ES was not anticipated prior to treatment initiation, and one received partial resection and spinal decompression as first therapy because the patient required immediate symptomatic relief.

Local therapy consisted of surgery (33), RT (17), or surgery and RT (17). Median tumor size among patients treated with surgery alone was 8.0 cm (range, 1.3–18 cm), with RT alone being 5.8 cm (range, 3.7–28.3), and with both surgery and RT being 8.4 cm (range, 3.8–28). Differences in sizes between local treatment groups were not statistically significant. Among pelvic tumors, 83% (10/12) received RT as a component of local therapy and only 17% (2/12) received surgery alone; among

Table 1. Patient characteristics for localized Ewing sarcoma patients treated with curative intent vincristine, doxorubicin, cyclophosphamide, and ifosfamide, etoposide chemotherapy ($n = 67$)

Patient characteristics	n (%)
Treating institution	
Dana-Farber Cancer Institute/Brigham and Women's Hospital	38 (57)
Massachusetts General Hospital	29 (43)
Age (years)	
<26	27 (40)
≥26	40 (60)
<40	54 (81)
≥40	13 (19)
Gender	
Male	27 (40)
Female	40 (60)
Primary tissue type	
Extraosseous	31 (46)
Osseous	36 (54)
Primary site of disease	
Pelvis	12 (18)
Extremity	29 (43)
Other	26 (39)
Size (cm)[a]	
<8	33 (52)
≥8	31 (48)
Local therapy	
Radiation therapy	17 (25)
Surgery	33 (50)
Both	17 (25)
Final pathology margins[b]	
Negative	37 (74)
Positive	13 (26)
Total number of definitive-intent chemotherapy cycles	
<14	27 (40)
≥14	40 (60)
Treatment sequence	
Initial induction chemotherapy	47 (71)
Initial local therapy	20 (29)

[a]Three patients did not have tumor size recorded.
[b]Seventeen patients who did not receive surgery were excluded.

extremity tumors, 79% (23/29) were treated with surgery alone. Among patients who received RT only as local therapy, the median dose was 57.6 Gy (range, 45–68.4). Among patients who received RT and surgery, the median dose was 54 Gy (range, 45–60). Among patients who underwent surgery, 74% had negative margins. Eleven of 13 patients with positive margins received RT.

Four patients underwent RT without concurrent chemotherapy; their tumors were located in the central nervous system (two), pelvis (one), and deep trunk (one), respectively. The

two patients with tumors in brain parenchyma received initial surgery followed by cranial-spinal RT; chemotherapy was held during RT due to toxicity concerns and was delivered following local therapy. The patient with a pelvic tumor received chemotherapy prior to and following RT. The patient with a retroperitoneal tumor received two cycles of induction chemotherapy but experienced severe toxicity such that systemic therapy was discontinued.

Response and Patterns of Failure

Thirty-five of 42 (83%) patients with an extraosseous component of disease who were treated with initial induction chemotherapy were evaluable for radiographic response to chemotherapy prior to local therapy. Among these 35 evaluable patients, 2 (6%) had complete response, 28 (80%) had partial response, and 5 (14%) had stable disease.

Six patients experienced disease progression during treatment (four during adjuvant chemotherapy, one after surgery, one during RT); tumor sites were pelvis (two), spine (two), deep trunk (one), and extremity (one). Fifteen patients experienced recurrence, and 15 died. Among the 15 patients who had recurrence, the site of first recurrence was local for 3, local and distant for 2, and distant for 10.

LRFS

Among the 61 patients who did not experience disease progression during treatment, there were 5 local recurrences (LR) as first site of recurrence and 2 LRs following DR. The median time to LR was 1.2 years (range, 0.9–2.3). As shown in Figure 1A, 5-year LRFS for all patients was 91% (95% confidence interval [CI]: 80%–96%). Five-year LRFS for patients with primary pelvic disease ($n = 10$) was 64% (95% CI: 23%–87%) and for nonpelvic primary disease ($n = 51$) was 96% (95% CI: 84%–99%, $p = .003$). Among patients with nonpelvic disease, 5-year LRFS for extremity ($n = 28$) was 96% (95% CI: 76%–99%) and for other (nonpelvis, nonextremity, $n = 23$) was 95% (95% CI: 72%–99%; $p = .01$). There were too few LR events to perform a multivariate analysis.

Survival (PFS and OS)

Among our 67 patients, there were 21 events. Median time to progression was 1.5 years (range: 0.5–5.3 years), Figure 1B. Five-year PFS was 66% (95% CI: 52%–77%). Five-year PFS for pelvic site was 27%, for extremity was 78%, and for other sites was 69%, ($p = .02$). PFS according to local treatment modality showed borderline statistical significance ($p = .05$); 5-year PFS for patients treated with RT was 44%, with surgery was 64%, and with both was 88%. On univariate analysis, there was no difference in PFS according to age, gender, tumor tissue type (osseous vs. extraosseous), tumor size, margin status, or treatment sequence (Table 2).

Multivariate analysis showed patients with pelvic primary had a 3.3 times increased risk of progression/recurrence compared with nonpelvic primary sites (hazard ratio [HR]: 3.3, 95% CI: 1.3–8.3, $p = .01$). In a second model, pelvic primary had a 4.4 times increased risk of progression/recurrence compared with extremity primary (HR: 4.4, 95% CI: 1.5–13.4, $p = .008$).

Among the 67 patients, 15 died. Median time to death was 2.4 years (range, 0.6–7.6). As shown in Figure 1C, 5-year OS rate was 79% (95% CI: 65%–87%). No patient characteristics

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A

B

C
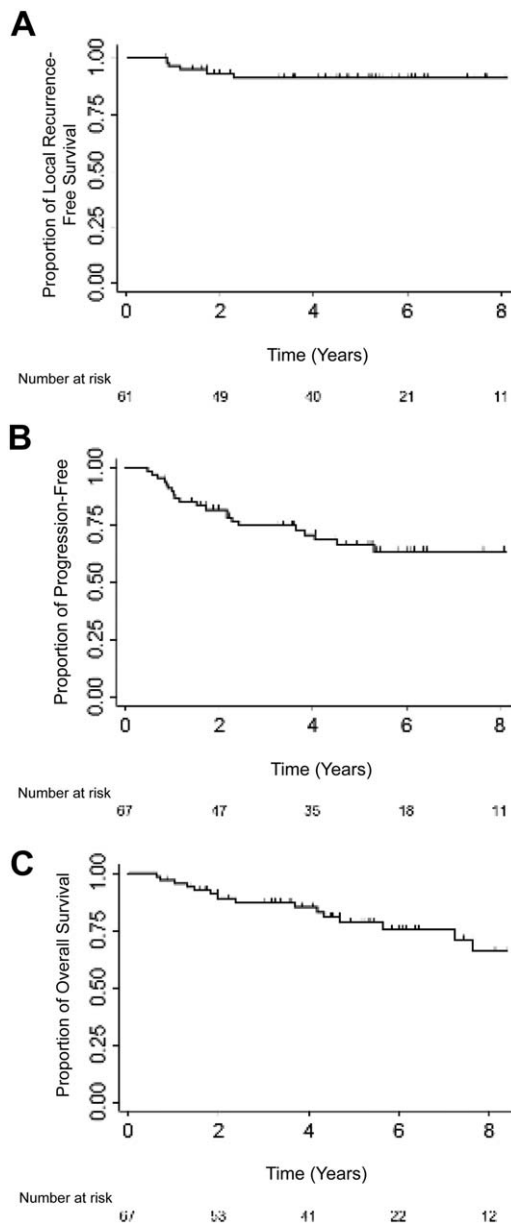
Figure 1. Kaplan-Meier plots for local recurrence-free survival **(A)**, progression-free survival **(B)**, and overall survival **(C)**.

Table 2. Univariate predictors for PFS and OS

Predictor	5-year PFS	p value	5-year OS	p value
Age (years)				
< 26	62%	p = .36	78%	p = .64
≥26	69%		79%	
Age (years)				
<40	62%	p = .19	75%	p = .19
≥40	84%		92%	
Gender				
Female	74%	p = .49	86%	p = .42
Male	61%		74%	
Primary tissue type				
Extraosseous	73%	p = .70	79%	p = .76
Osseous	61%		79%	
Primary site				
Pelvis	27%	p = .01	56%	p = .19
Nonpelvis	74%		83%	
Primary site				
Extremity	78%	p = .02	87%	p = .19
Pelvis	27%		56%	
Other	69%		78%	
Tumor size				
<8 cm	72%	p = .92	86%	p = .83
≥8 cm	68%		73%	
Local modality				
Radiation	44%	p = .05	88%	p = .38
Surgery	64%		71%	
Both	88%		87%	

Abbreviations: OS, overall survival; PFS, progression-free survival.

were prognostic for OS on univariate analysis (Table 2). Although only associated with borderline statistical significance, multivariate analysis showed pelvic primary had a 3.3 times increased risk of death compared with extremity primary (HR: 3.3, 95% CI: 0.8–13.4, p = .09).

DISCUSSION

To our knowledge, this is the largest series of adults with localized ES treated with VDC/IE chemotherapy. We report 5-year OS of 79%. This compares favorably with 5-year OS rates reported in historical series, which range from 20%–60% [9–14]. The previously reported 5-year OS for adults with localized disease from our institution was 49% [13]. This dramatic improvement is largely attributed to the use of VDC/IE as part of treatment. All the patients in our prior series received either no or alternative chemotherapy. A recent series by Ahmed

et al. [15] demonstrated that treatment era was an independent prognostic factor for survival. They compared outcomes of adults with localized ES treated between 1977–1992 and 1993–2007. The modern-era cohort was comprised of 52 patients, of whom 83% received VDC/IE, a population quite similar to the group reported herein. Five-year OS was 49% for patients treated between 1977–1992 and 73% for those treated between 1993–2007.

Usage of VDC/IE in adults began as an extrapolation from the data-driven pediatric experience [2–6]. Although these trials allowed enrollment of adults, they had relatively small numbers ≥18 years old, ranging from 9%–15% of study populations. It has been hypothesized by some investigators that adults with ES do worse than their pediatric counterparts and perhaps have tumors with inherently different biologies [9, 18]. Subgroup analyses within some prospective trials have demonstrated worse outcomes for older patients [2, 4–6], with 5-year event-free survival reported as 44%–47% for patients ≥18 [4, 6]. However, the trials that established VDC/IE as the standard regimen report 5-year OS ranging from 72%–83% across the study population [4, 6], and with such small numbers of adults included, power to make conclusions for this subgroup is limited. The 5-year OS of 79% reported herein and the recent 5-year OS of 73% reported by Ahmed [15] are in pure adult populations and are consistent with survival rates reported for

recent (predominantly pediatric) trials. Furthermore (in this issue of *The Oncologist*), Wagner [19] reports favorable 68% 5-year OS for 42 adults with localized ES treated with a vincristine, ifosfamide, and doxorubicin chemotherapy backbone. These similar survival rates suggest, with modern-era systemic therapy, ES in adults may have comparable outcome to children. It is also worth noting that results from retrospective single institutions trials are often favorable; accordingly, it will be important to confirm these outcomes in adults with ES in a prospective multicenter setting.

Age was not a significant prognostic factor in the present study. Although some prior reports have also reported no survival differences between older and younger adults [11, 14, 20], others have suggested a significant adverse outcome for older patients [2, 4, 6, 10, 21, 22].

Both size and location of primary tumor have been proposed as predictors of survival for ES. In this study, only pelvic site of disease had worse outcomes. Many prior reports have shown similar adverse prognosis for pelvic sites [2, 6, 21–23], although others have failed to show this difference [13, 15, 24, 25]. In our analysis, there was no difference in outcomes for tumor size $\geq$8 cm compared with <8 cm. Although there generally is more agreement in the literature with respect to large tumor size portending a poorer outcome [8, 10, 11, 23], the definition of tumor bulk is variable, and size may be correlated with tumor location.

The 5-year LR rate in this series was 9%; this is comparable to the LR rates reported in other studies, which range from 7%–15% [2–6, 15]. The most recent randomized study by Womer reported LR rates of 7%–8% [6], while the adult retrospective study published by Ahmed reported 14% [15]. No prospective trial has directly compared surgery to radiation, thus choice of local therapy is appropriately based on patient and tumor characteristics in an effort to minimize morbidity. Some series suggest better local control with surgery [5, 14, 15, 20, 26, 27], but others suggest no difference between the two modalities [21]. These series may be prone to inherent biases in patient selection in that larger, less resectable tumors are more likely treated with RT. However, because of risk of second malignancy and other late effects following RT, surgery is often the preferred modality if feasible with acceptable morbidity,

particularly for children and young adults [8]. Consistent with this thinking, Ahmed et al. report an increased utilization of surgery over time [15].

Conclusion

We report outcomes and prognostic factors for 67 adults with localized ES treated with VDC/IE-based multimodality therapy. Although this is retrospective, it is the largest series of adults treated exclusively with chemotherapy considered standard of care for pediatric patients. PFS and OS rates are excellent, are better than historical outcomes for adults, and are comparable to current pediatric outcomes. We also report very good local control following treatment with a mix of surgery and RT; we do not support one local modality as superior to the other and encourage continued case-specific choices in this regard. Consistent with pediatric literature, pelvic location is an adverse predictor for PFS and OS, such that these patients could benefit from alternative treatment strategies or treatment intensification.

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Editor's Note:

See the companion paper, "Vincristine, Ifosfamide, and Doxorubicin for Initial Treatment of Ewing Sarcoma in Adults," by Michael J. Wagner, Vanceswaran Gopalakrishnan, Vinod Ravi et al., on page 1271 of this issue.

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