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Perspective

Chemotherapeutic Treatment of Localized Ewing's Sarcoma in Adults

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Perspective

Ewing's sarcoma is a rare bone tumor that is typically identified as a small, round, blue cell neoplasm. It primarily presents in children and adolescents with few cases occurring in adults over 30 years of age. Ewing's sarcomas tend to arise in the long bones of extremities as well as bones of the pelvis with a minority being extra osseous [1]. Genetically, Ewing's sarcomas are defined by recurrent translocations on chromosome 22q12, the EWSR1 gene, with over 85% of cases involving the EWSR1-FLI1 fusion gene [2]. Treatment outcomes for Ewing's have improved markedly in the modern era and over 70% of patients can be cured of their disease [3]. However, most patients enrolled in the large Ewing's trials are children under the age of 18 and there is a paucity of data regarding management for young and old adults. In this perspective, we will discuss the data regarding the treatment of Ewing's sarcoma in adults over the age of 18 and our own institutional treatment recommendations.

Modern treatment plans for Ewing's involve multimodality therapy with neoadjuvant chemotherapy, followed by definitive local treatment, followed by additional adjuvant chemotherapy. Ewing's is considered a systemic disease and patients are assumed to have subclinical metastases at diagnosis, necessitating chemotherapy as an essential part of the treatment regimen. The current standard of care in adults is the regimen of Vincristine, Doxorubicin, and Cyclophosphamide (VDC) alternating with Ifosfamide and Etoposide (IE) every 3 weeks for 17 cycles. This was established in a landmark 2003 study that compared vincristine, doxorubicin, cyclosphosphamide, and dactinomycin (VACA) compared with these four drugs alternating with Ifosfamide and Etoposide (IE) [4]. In localized patients, additional IE therapy led to significant improvements in 5-year event free survival (EFS 69% *vs.* 54%) and 5-year overall survival (OS 72% *vs.* 61%). In 2012, further intensification of therapy was studied by the Children's Oncology group in a randomized control trial, with interval-compressed chemotherapy VDC/IE every two weeks instead of three [5]. This time intensification led to a significantly improved 5-year EFS (73% *vs.* 65%) and a non-significantly improved 5-year OS (83% *vs.* 77%) [5]. This trial actually enrolled patients up to the age of 45, however, patients over the age of 18 had considerably worse outcomes with a 5-year EFS of 47% *vs.* 72%. Therefore, in children under the age of 18, the preferred regimen for localized Ewing's sarcoma is VDC/IE q2 weeks for 14 cycles.

Data for adults in Ewing's sarcoma is more sparse and relies on small retrospective cohort studies and subgroup analyses of large trials. For example, a retrospective single center report from Memorial Sloan-Kettering Cancer Center (MSKCC) identified only 59 adult Ewing's patients (age>16) out of 4,677 adult sarcoma patients seen during an 18 year time period from 1982-2000 () [6]. In addition, across studies there is no consistent age threshold for adult with some studies using 16, others 18, and some as high as 30 or 40. Multiple studies have shown that adults have worse prognosis than children or young adolescents (Table 1). A large retrospective SEER study in 2017 looked at the differences between all pediatric and adult (≥18 years of age) Ewing's sarcomas diagnosed between the years 1983-2013 [7]. In a cohort of 1,870 patients (976 pediatric and 894 adult), they found that adults were significantly more likely to be metastatic at diagnosis (33% *vs.* 26%) and to have worse outcomes (5-year OS 43% *vs.* 66%). Due to lack of chemotherapy data in the SEER registry, it was unclear how often adults received chemotherapy or what regimens were used. Another SEER study in 2013 looked at Ewing's adults over the age of 40 compared to younger patients and again found higher rates of extra-skeletal tumors (66.1% *vs.* 31.7%), metastatic disease (35.5% *vs.* 30%), and inferior overall survival (5-year OS of 30.6% *vs.* 54.3%) [8]. In the seminal paper that established IE to the VDC backbone, adults were found to have significantly worse outcomes with 5-year EFS for patients <10 years, between 10-17 years, and ≥ 18 years of age being 70%, 60%, and 44% respectively [4]. There was no difference in dose intensity of chemotherapy between age groups, suggesting that the difference in outcome was due more to inherently worse biology rather than age-related intolerance of chemotherapy. Other small retrospective studies have described a 5-year OS for adult Ewing's patients around 37-60%. This is in contrast to pediatric/adolescent patients who have a 5 year OS around 70% [1,9-12].

Current treatment of adult Ewing's patients mirrors that used in children and adolescents. There is a lack of rigorous, randomized, prospective data comparing treatment regimens solely in adults and most data is derived from retrospective single center studies. For localized patients, evidence suggests that aggressive pediatric-like regimens produce better outcomes in adults compared to less intensive regimens. A retrospective analysis of 102 localized adult Ewing's patients (age range 18-60) seen at the Mayo Clinic from 1977-2007 found a total cohort 5-year OS and EFS of 60% and 52% respectively [13]. Outcomes were subsequently compared based on a split from 1977-1992 (Group A) and 1993-2007 (Group B), due to the uniform adoption of Ifosfamide/Etoposide (IE) chemotherapy after the Intergroup-0091 trial. In Group A, only 12% of patients received IE chemotherapy versus 88% in Group B. The resulting differences in survival were marked, with a 5-year OS of only 49% in Group A and 73% in Group B, a survival rate approaching those seen in children. The same principle seems to hold true for metastatic patients: a retrospective review of 36 metastatic adult Ewing's patients showed

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Table 1: Multiple studies on adults and children or young adolescents.

Study	# Patients	Median Age	% Metastatic at Diagnosis	5 year OS
Verrill 1997[19]	59	24	29%	38%
Fizazi 1998[20]	182	21.5	29%	41%
Baldini 1999[21]	37	26	30%	37%
Martin 2003[6]	59	27	13%	60%
Bacci 2007[15]	35	48	0%	46%
Ahmed 2013[13]	102	28	0%	60%
Karski 2013[8]	383	53.7	35.50%	43.40%
Verma 2017[7]	894	29	33%	43%

the superiority of the VDC/IE regimen with a 4 year OS of 26% *vs.* 14% for other regimens [14]. However, adults have a harder time tolerating intensive chemotherapy and experience more frequent dose delays and reductions as well as chemotherapy related complications. A retrospective review compared localized Ewing's patients age 40 and over (n=35) with patients age 39 and younger (n=586) and found significantly lower dose intensity compliance (46.7% *vs.* 74.1%) as well as significantly higher grade 4 hematologic toxicity (22.8% *vs.* 16%) and need for hospitalization (7.4% *vs.* 1.9%) [15].

At our own institution, we treat all localized Ewing's sarcoma adults under the age of 60 with VDC/IE alternating every 3 weeks with local treatment after the 4th cycle and subsequent consolidation chemotherapy given for a total of [14-17] cycles. For adults over the age of 60, we substitute IE with irinotecan/temozolomide. The dosing is irinotecan IV 40mg/m^2 D1-5 and temozolomide PO 100mg/m^2 D1-5 every 3 weeks. Previous studies have established the effectiveness of irinotecan and temozolomide in recurrent/progressive Ewing's with response rates around 50-70% [16-18]. In our experience, this is better tolerated than IE, can be given in the outpatient setting, and has comparable efficacy. Careful attention must be paid to side effects such as diarrhea, which is a well-known toxicity to irinotecan and can limit dosing.

In summary, Ewing's sarcoma in adults is a rare entity that has a worse prognosis than children and young adolescents. However, adults appear to benefit from more aggressive pediatric-like chemotherapy regimens albeit at higher toxicity cost. We recommend that new diagnosis localized adult Ewing's patients be considered to have full dose VDC/IE every 3 weeks with individualized adjustments based on other medical comorbidities and performance status. Over the age of 60, we substitute irinotecan/temozolomide for IE.

References

1. Raney RB, Asmar L, Newton WA, Bagwell C, Breneman JC, Crist W, et al. Ewing's sarcoma of soft tissues in childhood: a report from the Intergroup Rhabdomyosarcoma Study, 1972 to 1991. J. Clin. Oncol. 1997; 15: 574-582.
2. Delattre O, Zucman J, Melot T, Garau XS, Zucker JM, Lenoir GM, et al. The Ewing family of tumors--a subgroup of small-round-cell tumors defined by specific chimeric transcripts. N. Engl. J. Med. 1994; 331: 294-299.
3. Granowetter L, Womer R, Devidas M, Krailo M, Wang C, Bernstein M, et al. Dose-intensified compared with standard chemotherapy for nonmetastatic Ewing sarcoma family of tumors: a Children's Oncology Group Study. J. Clin. Oncol. 2009; 27: 2536-2541.
4. Grier HE, Krailo MD, Tarbell NJ, Link MP, Fryer CJ, Pritchard DJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. N. Engl. J. Med. 2003; 348: 694-701.
5. Womer RB, West DC, Krailo MD, Dickman PS, Pawel BR, Grier HE, et al. Randomized Controlled Trial of Interval-Compressed Chemotherapy for the Treatment of Localized Ewing Sarcoma: A Report From the Children's Oncology Group. J. Clin. Oncol. 2012; 30: 4148-4154.
6. Martin II RCG, Brennan MF. Adult Soft Tissue Ewing Sarcoma or Primitive Neuroectodermal Tumors. Arch. Surg. 2003; 138: 281.
7. Verma V, Denniston KA, Lin CJ, Lin C. A Comparison of Pediatric *vs.* Adult Patients with the Ewing Sarcoma Family of Tumors. Front. Oncol. 2017; 7: 82.
8. Karski EE, Matthay KK, Neuhaus JM, Goldsby RE, Dubois SG. Characteristics and outcomes of patients with Ewing sarcoma over 40 years of age at diagnosis. Cancer Epidemiol. 2013; 37: 29-33.
9. Paulussen M, Ahrens S, Dunst J, Winkelmann W, Exner GU, Kotz R, et al. Localized Ewing tumor of bone: final results of the cooperative Ewing's Sarcoma Study CESS 86. J. Clin. Oncol. 2001; 19: 1818-1829.
10. Craft A, Cotterill S, Malcolm A, Spooner D, Grimer R, Souhami R, et al. Ifosfamide-containing chemotherapy in Ewing's sarcoma: The Second United Kingdom Children's Cancer Study Group and the Medical Research Council Ewing's Tumor Study. J. Clin. Oncol. 1998; 16: 3628-3633.
11. Obata H, Ueda T, Kawai A, Ishii T, Ozaki T, Abe S, et al. Clinical outcome of patients with Ewing sarcoma family of tumors of bone in Japan: the Japanese Musculoskeletal Oncology Group cooperative study. Cancer. 2007; 109: 767-775.
12. Rodríguez-Galindo C, Liu T, Krasin MJ, Wu J, Billups CA, Daw NC, et al. Analysis of prognostic factors in ewing sarcoma family of tumors: review of St. Jude Children's Research Hospital studies. Cancer. 2007; 110: 375-384.
13. Ahmed SK, Robinson SI, Okuno SH, Rose PS, Laack NN. Adult ewing sarcoma: survival and local control outcomes in 102 patients with localized disease. Sarcoma. 2013.
14. Ahmed SK, Robinson SI, Okuno SH, Rose PS, Issa Laack NN. Adult Ewing Sarcoma. Am. J. Clin. Oncol. 2014; 37: 423-429.
15. Bacci G, Alba Balladelli MD, Cristiana Forni RN, Stefano Ferrari MD, Alessandra Longhi MD, Patrizia Bacchini MD, et al. Adjuvant and neoadjuvant chemotherapy for Ewing sarcoma family tumors in patients aged between 40 and 60. Cancer. 2007; 109: 780-786.
16. Wagner LM, McAllister N, Goldsby RE, Rausen AR, McNall-Knapp RY, McCarville MB, et al. Temozolomide and intravenous irinotecan for treatment of advanced Ewing sarcoma. Pediatr. Blood Cancer. 2007; 48: 132-139.
17. Raciborska A, Bilska K, Drabko K, Chaber R, Pogorzala M, Wyrobek E, et al. Vincristine, irinotecan, and temozolomide in patients with relapsed and refractory Ewing sarcoma. Pediatr. Blood Cancer. 2013; 60: 1621-1625.
18. Casey DA, Wexler LH, Merchant MS, Chou AJ, Merola PR, Price AP, et al. Irinotecan and temozolomide for Ewing sarcoma: The Memorial Sloan-Kettering experience. Pediatr. Blood Cancer. 2009; 53: 1029-1034.
19. Verrill MW, Judson IR, Harmer CL, Fisher C, Thomas JM, Wiltshaw E. Ewing's sarcoma and primitive neuroectodermal tumor in adults: are they different from Ewing's sarcoma and primitive neuroectodermal tumor in children? J. Clin. Oncol. 1997; 15: 2611-2621.
20. Fizazi K, Dohollou N, Blay JY, Guérin S, Le Cesne A, André F, et al. Ewing's family of tumors in adults: multivariate analysis of survival and long-term results of multimodality therapy in 182 patients. J. Clin. Oncol. 1998; 16: 3736-3743.
21. Baldini EH, Demetri GD, Fletcher CD, Foran J, Marcus KC, Singer S. et al. Adults with Ewing's sarcoma/primitive neuroectodermal tumor: adverse effect of older age and primary extraosseous disease on outcome. Ann. Surg. 1999; 230: 79-86.