Expanded Access Through Cancer Trials Support Unit to Children's Oncology Group Sarcoma Trial AEWS1031 for Adolescents and Young Adults

Leo Mascarenhas, MD, MS,¹ Mason C. Bond, MD,² and Nita L. Seibel, MD³

Official trial name: A Phase III Randomized Trial of Adding Vincristine–Topotecan–Cyclophosphamide to Standard Chemotherapy in Initial Treatment of Non-metastatic Ewing Sarcoma

ClinicalTrials.gov Identifier: NCT01231906 www.clinicaltrials.gov/ct2/show/NCT01231906

COG Study Chair: Mason C. Bond, MD
COG Study Vice-Chair: Leo Mascarenhas, MD, MS
RTOG Study Co-Chair: Dian Wang, MD, PhD

EWING SARCOMA FAMILY OF TUMORS (ESFT) is the second most common malignant tumor of bone and occurs predominantly in the adolescent and young adult age group.¹ They include Ewing sarcoma, atypical Ewing sarcoma, and peripheral primitive neuroectodermal tumor of bone. Even though this malignancy arises mainly from the bone, primary extraosseous tumors also occur. These tumors are believed to be of neural crest origin and occur with almost equal incidence in the extremities and central axial sites. There is a dramatic racial variation in incidence, with almost no discernable incidence in individuals of African and Asian or Pacific island descent. Other than race, there are no known risk factors for ESFT. A EWS-ETS fusion protein is characteristic of ESFT, with over 85% of tumors expressing the EWS-FLI-1 fusion transcript.²

ESFT are primarily treated with chemotherapy, surgery, and radiotherapy. ESFT are radiosensitive tumors and radiation is primarily used for local tumor control in patients with unresectable primaries, involved surgical margins, certain metastatic sites, and sometimes, large tumors with a poor histological response to chemotherapy.³

Vincristine, doxorubicin, cyclophosphamide, and actinomycin-D (VDCA) were investigated in the first two Intergroup Ewing's Sarcoma Studies (IESS). IESS-1 demonstrated the importance of using doxorubicin in the treatment of patients with ESFT, whereas IESS-2 demonstrated the role of high-dose intermittent therapy.^{4,5} Based on promising phase II data with ifosfamide and etoposide (IE), a randomized phase

III intergroup trial (INT-0091) compared VDCA with VDCA alternating with IE. Among the 398 patients with non-metastatic disease, the mean 5-year event-free survival (EFS) among the 198 patients who received IE was $69\% \pm 3\%$, compared with $54\% \pm 4\%$ among the 200 patients in the standard therapy group ($P=0.005$). Overall survival was also significantly better among patients in the IE group ($72\% \pm 3.4\%$ vs. $61\% \pm 3.6\%$ in the standard therapy group; $P=0.01$).⁶ As a result of this trial, standard therapy for localized ESFT in North America now includes ifosfamide and etoposide in addition to VDC. The next intergroup trial, INT-0154, randomized patients between the new standard therapy of VDC alternating with IE and a regimen in which the doses of cyclophosphamide and ifosfamide were escalated to increase dose intensity. There was no significant difference ($P=0.57$) in EFS between the 231 patients treated with the standard therapy (5-year EFS=72.1%; 95% confidence interval, 65.8%–77.5%) or the 247 patients treated with the intensified regimen (5-year EFS=70.1%; 95% confidence interval, 63.9%–75%).⁷ The Children's Oncology Group (COG) next conducted a randomized controlled phase III trial (AEWS0031) that tested whether chemotherapy intensification by interval compression would improve the outcome of patients with non-metastatic disease. On this trial, patients received VDC alternating with IE every three weeks on the standard arm, whereas patients received the same chemotherapy every two weeks on the experimental arm. The median cycle interval on the standard arm was 21 days when compared with 15 days on the experimental arm for the 284 eligible

¹Keck School of Medicine, University of Southern California, Division of Hematology and Oncology, Children's Hospital Los Angeles, Los Angeles, California.

²Division of Oncology/Hematology/Bone Marrow Transplant, University of British Columbia, British Columbia Children's Hospital, Vancouver, British Columbia, Canada.

³Cancer Therapy Evaluation Program, Clinical Investigations Branch, National Cancer Institute, Bethesda, Maryland.

patients on each arm. EFS at a median of three years was 65% for those receiving standard therapy and 76% for those receiving experimental therapy ($P=0.028$).⁸

One strategy to improve the outcome of patients with cancer is to incorporate new agents into standard therapy. The combination of topotecan and cyclophosphamide is active in patients with metastatic and recurrent ESFT, with response rates between 33% and 57%.^{9–11} With the objective of conducting a randomized phase III trial incorporating topotecan and cyclophosphamide with interval compressed therapy, COG conducted a pilot study (AEWS07P1) that introduced vincristine, topotecan, and cyclophosphamide (VTC) to standard interval compressed therapy with VDC/IE. This trial showed that it was feasible and safe to give VTC with standard interval compressed therapy without increasing the toxicity (Mascarenhas L, Felgenhauer J, Bond M, *et al.* Pilot study of adding vincristine, topotecan and cyclophosphamide to interval compressed chemotherapy in newly diagnosed patients with localized Ewing sarcoma family of tumors—A Children's Oncology Group trial [manuscript in preparation]).

The featured clinical trial—COG AEWS1031—will randomize patients with newly diagnosed non-metastatic ESFT between standard interval-compressed VDC/IE and the experimental arm consisting of interval-compressed therapy with the addition of VTC (VTC/VDC/IE). The primary objective is to evaluate the effect of the experimental regimen on EFS and overall survival. Patients less than 50 years of age will be eligible based on institutional pathologic diagnosis. Patients must have adequate renal, liver, and cardiac function.

Therapy will consist of 17 cycles of chemotherapy on both arms. The study, designed to show an improvement in EFS from 70% to 80% with 80% power, has an estimated accrual time of 4.5 years for a sample size of 630 patients. Local control of the tumor will be decided by the treating physician.

The Cancer Trials Support Unit (CTSU) webpage (www.CTSU.org), a service of the National Cancer Institute (NCI), provides clinicians in the United States and Canada with access to cancer treatment trials conducted by cooperative study groups of which they or their institution are not members. Started in 1999 with patient enrollment beginning in 2000, CTSU is funded and directed by the NCI Cancer Therapy Evaluation Program and operated by Westat and the Coalition of Cancer Cooperative Groups. CTSU provides a wide choice of clinical trial options to the largest possible number of investigators. All NCI cooperative groups are members, including COG. Nearly all phase III treatment trials in breast, gastrointestinal, genitourinary, and lung cancers, as well as adult leukemia, are available through CTSU. In addition, clinical trials are also offered for gynecological, sarcoma, pancreatic, and other cancer diagnoses. For a trial to be available through CTSU, at least one other cooperative group must support the trial. Investigators from all the NCI cooperative groups have access to CTSU and can download the posted protocol, submit it to their local institutional review board (IRB) for approval, and then activate the trial. Once the patient has signed the informed consent document, enrollment onto the trial as well as all data submission is also made through the CTSU.

AEWS1031 trial is the first COG trial available through CTSU. This was made possible through the collaboration and

support of the Radiation Therapy Oncology Group. The criteria for determining which COG trials will be available through CTSU are whether the age range includes adolescents and young adults who may be treated by medical oncologists and ensuring that the proposed studies do not overlap with protocols currently available through CTSU. The eligibility for AEWS1031 is up to age 50 and is the only CTSU-available Ewing sarcoma protocol. This will enable oncologists who are not members of COG to enroll patients with newly diagnosed ESFT. To be available through CTSU, the NCI's pediatric central IRB has included medical oncologists as part of the review process. This enables institutions who participate in either the pediatric or adult central IRB to activate it following their local IRB guidelines for new protocols. This is an example of one of the ways in which the NCI and the cooperative groups are striving to improve the outcome for adolescent and young adult patients with cancer by providing access to clinical trials.

References

1. Mascarenhas L, Siegel S, Spector L, *et al.* Malignant bone tumors in adolescents and young adults. In: Cancer epidemiology in older adolescents and young adults 15–29 years of age, including SEER incidence and survival: 1975–2000 (NIH Pub. No. 06-5767). Bleyer A, O'Leary M, Barr R, Ries LAG (Eds); Bethesda, MD: National Cancer Institute; 2006; pp. 97–110.
2. Ladanyi M, Lewis R, Garin-Chesa P, *et al.* EWS rearrangement in Ewing's sarcoma and peripheral neuroectodermal tumor. Molecular detection and correlation with cytogenetic analysis and MIC2 expression. *Diagn Mol Pathol.* 1993;2: 141–146.
3. Bernstein ML, Kovar H, Pauussen M, *et al.* Ewing Sarcoma Family of Tumors: Ewing Sarcoma of Bone and Soft Tissue and the Peripheral Primitive Neuroectodermal Tumors. In: *Principles and Practice of Pediatric Oncology* (5th Edition). Pizzo PA, Poplack DG (Eds); Philadelphia: Lippincott Williams & Wilkins; 2005; pp. 1002–1032.
4. Nesbit ME, Gehan EA, Burgert EO, *et al.* Multimodal therapy for the management of primary, non-metastatic Ewing's sarcoma of bone: a long-term follow-up of the First Intergroup study. *J Clin Oncol.* 1990;8:1664–1674.
5. Burgert EO, Nesbit ME, Garnsey LA, *et al.* Multimodal therapy for the management of nonpelvic, localized Ewing's sarcoma of bone: intergroup study IEWS-II. *J Clin Oncol.* 1990;8:1514–1524.
6. Grier HE, Krailo MD, Tarbell NJ, *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.
7. Granowetter L, Womer R, Devidas M, *et al.* Dose-intensified compared with standard chemotherapy for non-metastatic Ewing sarcoma family of tumors: a Children's Oncology Group Study. *J Clin Oncol.* 2009;27:2536–2541.
8. Womer RB, West D, Krailo MD, *et al.* Randomized comparison of every-two-week v. every-three-week chemotherapy in Ewing sarcoma family tumors (ESFT) [abstract]. *J Clin Oncol.* 2008;26:554a.
9. Bernstein ML, Devidas M, Lafreniere D, *et al.* Intensive therapy with growth factor support for patients with Ewing tumor metastatic at diagnosis: Pediatric Oncology Group/Children's Cancer Group phase II study 9457—a report from

- the Children's Oncology Group. *J Clin Oncol*. 2006;24:152–159.
10. Saylor RL, Stine KC, Sullivan J, *et al*. Cyclophosphamide plus topotecan in children with recurrent or refractory solid tumors: a Pediatric Oncology Group phase II study. *J Clin Oncol*. 2001;19:3463–3469.
 11. Hunold A, Weddeling N, Paulussen M, *et al*. Topotecan and cyclophosphamide in patients with refractory or relapsed Ewing tumors. *Pediatr Blood Cancer*. 2006;47:795–800.

Address correspondence to:
Leo Mascarenhas, MD, MS
Keck School of Medicine
University of Southern California
Division of Hematology and Oncology
Children's Hospital Los Angeles
4650 Sunset Blvd., Mailstop # 54
Los Angeles, CA 90027

E-mail: lmascarenhas@chla.usc.edu