Published in final edited form as:

Pediatr Blood Cancer. 2012 October ; 59(4): 611–616. doi:10.1002/pbc.24031.

Predictors of Acute Chemotherapy-Associated Toxicity in Patients with Ewing Sarcoma

Jeremy M. Sharib, BS¹, Jobin Cyrus, MPH¹, Andrew Horvai, MD, PhD², Florette K. Gray Hazard, MD³, John Neuhaus, PhD⁴, Katherine K. Matthay, MD¹, Robert Goldsby, MD¹, Neyssa Marina, MD⁵, and Steven G. DuBois, MD¹

¹Department of Pediatrics, University of California, San Francisco School of Medicine, San Francisco, California

²Department of Pathology, University of California, San Francisco

³Department of Pathology, Stanford University School of Medicine, Palo Alto, CA

⁴Department of Biostatistics, University of California, San Francisco

⁵Department of Pediatrics, Stanford University School of Medicine

Abstract

Background—Ewing sarcoma (ES) is a malignant tumor of bone and soft tissue of children and young adults. Patients with ES are treated with intensive chemotherapy regimens. We describe predictors of acute chemotherapy-associated toxicity in this population.

Procedure—In this retrospective cohort study, records of ES patients treated at two academic medical centers between 1980 and 2010 were reviewed. Grade 3 and 4 non-hematologic chemotherapy-associated toxicities during frontline therapy were recorded for each patient, along with potential clinical and demographic predictors of toxicity. Bivariate analyses were performed using the Fisher exact test. Multivariate analysis was performed using logistic regression.

Results—The cohort included 142 patients with ES and toxicity data. In bivariate analyses, age <12 years at diagnosis, Latino ethnicity, low family income, and treatment on a clinical trial were associated with higher incidence of toxicity ($p < 0.01$). Tumor size, site, stage, mode of local control, body mass index, overall chemotherapy exposure and dose-intensity were not associated with toxicity. In multivariate analysis, low income (odds ratio (OR) 4.97, 95% CI 1.9–13.1), clinical trial enrollment (OR 3.67, 95% CI 1.2–10.9), pelvic tumor site (OR 3.88, 95% CI 1.17–12.88), and age <12 years (OR 2.8, 95% CI 1.0–7.5) were independent predictors of toxicity.

Conclusion—ES patients who are younger, of Latino ethnicity, have pelvic tumors or low income have higher rates of toxicity that may require increased supportive care. Treatment on a clinical trial was also associated with higher rates of toxicity, though this finding may reflect better reporting in these patients.

Keywords

Ewing sarcoma; toxicity; income; ethnicity; age

Corresponding Author: Steven G. DuBois, MD, Department of Pediatrics, UCSF School of Medicine, 505 Parnassus Avenue, M646, San Francisco, CA 94143-0106, Telephone: 415-476-3831, Facsimile: 415-502-4327, dubois@peds.ucsf.edu.

Disclosures: None

Introduction

Ewing sarcoma (ES) is the second most common primary bone cancer in children and adolescents [1,2]. Patients with localized or metastatic ES are treated with intensive multiagent chemotherapy, and more recent trends have increased individual drug doses and dose intensity [3,4]. Patients also require local control measures directed at the primary tumor, typically with surgery, radiation, or surgery plus radiation. This multimodality therapy results in significant toxicity both for patients with metastatic and localized disease [4–7].

Predictors of chemotherapy toxicity have not been well characterized in patients with ES. In other childhood malignancies, key predictors of toxicity identified previously have included: chemotherapy dose and dose-intensity [8,9]; high BMI [10–11]; pretreatment bilirubin [12]; renal function [13]; and genetic polymorphisms in enzymes involved in chemotherapy metabolism [14,15]. Young age as a predictor of toxicity remains inconclusive [9].

Comparisons of toxicity by race have shown that white children experience less neurotoxicity from vincristine [16], and less hypothyroidism after treatment for lymphoma when compared to black patients [17]. Furthermore, variable clearance of a number of drugs used to treat childhood cancer has been reported between racial and ethnic groups. For example, black and white children differ in clearance of methotrexate and cytarabine [18,19] while Latino children did not show a significant difference compared to white children [19]. Additional studies have shown that white, non-Latino children have lower rates of treatment-related myelodysplastic syndrome/acute myelogenous leukemia (AML) compared to Latino patients [20–22].

Despite the above evidence, predictors of chemotherapy-associated toxicity have not been described for ES. The aim of the current study was to determine whether ethnicity, socioeconomic status, or other clinical variables correlate with acute toxicity to initial chemotherapy in patients with ES. We focused on non-hematologic toxicity since with contemporary ES therapy, high-grade myelosuppression is nearly universal [4]. The goal of this effort was to identify subgroups of patients who might benefit from increased supportive care measures and to inform future pharmacogenomic studies in this disease.

Methods

Patient Population

The institutional review boards for both UCSF and Stanford University approved this retrospective cohort study. Clinical and pathology records at the University of California, San Francisco (UCSF) and Stanford University Medical Centers were searched using International Classification of Disease (ICD) codes to identify patients with ES. All patients with these tumors arising in bone, soft tissue, or viscera treated at either institution between 1980 and 2010 were eligible for the study. Patients seen only for clinical or pathology consultation without subsequent treatment at either institution were excluded. Clinical data were collected and adverse events were coded by a single reviewer (JS). Two pathologists (AH and FH) reviewed all available pathologic specimens to confirm the diagnosis of ES whenever possible.

Predictor and Outcome Variables

Patient demographics, disease characteristics at presentation, initial chemotherapy, clinical trial status, and local control modality were collected for each patient. Ethnicity was classified as either Latino or non-Latino based on ethnicity noted in the patient record, typically based on patient reported ethnicity. Patient race was also collected though not analyzed further due to small numbers of non-white patients, consistent with the known

epidemiology of this disease [23]. Data for a proxy for low family income (eligibility for California's state program for low income patients < 21 years of age) were also collected for all patients under 21 years of age at diagnosis.

Cumulative chemotherapy and dose-intensity during frontline chemotherapy were reviewed based on doses received by each patient. Dose-intensity for each drug was calculated using the formula [total dose/(date of last cycle+21 days – date chemotherapy started)/7] as previously described [6,24]. To account for differences in standard frontline chemotherapy regimens over the period analyzed, single cumulative chemotherapy and chemotherapy dose-intensity scores were constructed to normalize the data to the doses prescribed on the interval compressed arm of Children's Oncology Group protocol AEWS0031, a current standard North American regimen [25]. To obtain the cumulative dose score, the cumulative doses received for each agent were summed and divided by AEWS0031 doses for each respective agent. The cumulative dose ratios for all drugs received were then averaged. An average cumulative dose ratio less than 0.9 was considered low dose; a cumulative dose ratio between 0.9 and 1.1 was considered target dose; and a cumulative dose ratio above 1.1 was considered high dose. A similar approach was taken to calculate the dose-intensity score.

The primary outcome variable was grade 3 or 4 non-hematologic toxicities during frontline chemotherapy. Each patient was coded as either experiencing or not experiencing at least one grade 3 or 4 non-hematologic toxicity during the full treatment course of upfront therapy. Toxicity was graded for the current study according to the US National Cancer Institute's Common Toxicity Criteria for Adverse Events (CTCAE), version 3.0. Patients who received myeloablative chemotherapy with stem cell rescue as part of initial therapy were included in the analysis, though only toxicities experienced during non-myeloablative chemotherapy cycles were included. No toxicities associated with relapse or salvage chemotherapy were included, nor were any complications of surgical procedures. Toxicities occurring during concomitant administration of radiotherapy and chemotherapy were included.

Statistical Analysis

Potential clinical and demographic predictors of grade 3 or 4 non-hematologic toxicity were evaluated statistically using the Fisher exact test. No adjustment was made for multiple testing. Logistic regression was used to assess the independent contribution of bivariate predictors of toxicity, while controlling for potential confounders. The sample size was a convenience sample of patients with ES available for chart review at the two institutions. The possibility of interactions between covariates in the final model was assessed by serially adding interaction terms of pairs of covariates into the model. All statistical analyses were performed using SAS (version 9) and STATA (version 10).

Results

Patient Characteristics

Two hundred eighty-two patients were identified with a diagnosis of ES between 1980 and 2010, and 219 patients received treatment at either institution. Of this cohort, 77 patients had missing treatment records or were referred for BMT or relapse therapy only. The remaining 142 patients had available toxicity data following initial chemotherapy and thus were included for analysis. Demographic and clinical characteristics are shown in Table 1. Tumor and disease characteristics were typical for ES.

All patients received upfront combination chemotherapy that included at least three agents. Across the time range for this study, two standard clinical regimens for localized or

metastatic disease were typically used in these patients: vincristine, doxorubicin, cyclophosphamide, actinomycin-D (VDCA; n= 8; median treatment months= 11.4 [2.8–18.2]) and vincristine, doxorubicin, cyclophosphamide alternating with ifosfamide, etoposide (VDC/IE; n= 121; median treatment months= 9.41 [1.3–30.7]). Other combinations included an intensive regimen for patients with metastatic disease (VIDE; n= 3; median treatment months= 10.33 [10.2–11.4]) [5], investigational protocols including cytotoxic agents with a biologic agent (n= 5; median treatment months= 13.0 [5.1–18.4]), and other combinations of the above drugs (n= 5; median treatment months= 13.3 [11.3–17.8]). All but two patients received supportive care with myeloid growth factor according to standard practice at the time. Thirty-five patients (25%) were enrolled on clinical trials. When cumulative chemotherapy doses were directly compared to AEWS0031, 76 patients (66%) received higher average cumulative doses, while no patients received < 90% of the cumulative doses prescribed on AEWS0031. However, 58 (53%) patients received a lower dose-intensity compared to AEWS0031, likely because many of the patients were treated before widespread use of interval compressed dosing.

Chemotherapy Associated Non-Hematologic Toxicity

Ninety patients (63%) experienced at least one grade 3 or 4 non-hematologic toxicity during non-myeloablative chemotherapy cycles. Of these, 63 patients (70%) experienced more than one episode of grade 3 or 4 non-hematologic toxicity. Details of toxicities experienced are shown in Table 2, with each percentage corresponding to the proportion of patients with a given toxicity at any time throughout the course of upfront chemotherapy. Grade 3 febrile neutropenia (49%), infection (30%), and mucositis (7%) were the most prevalent high-grade toxicities. Grade 4 toxicities included febrile neutropenia (3%), infection (2%), and pulmonary embolism (1%).

Bivariate and Multivariate Predictors of Toxicity

The incidence of grade 3 or 4 non-hematologic toxicity according to potential predictor variables is shown in Table 3. Latino patients were more likely to experience grade 3 or 4 toxicity to upfront chemotherapy than non-Latino patients (82% vs. 56%; odds ratio for toxicity among Latino patients = 3.55; 95% CI 1.43 – 8.77; p = 0.006). Younger patients, diagnosed before the age of 12 years, experienced more grade 3 or 4 events than their older counterparts (79% vs. 59%; odds ratio for toxicity among younger patients = 2.93; 95% CI 1.31 – 6.57; p = 0.009). Age was also analyzed as a continuous variable with similar results. The mean age of patients who experienced grade 3 or 4 toxicity was 12.7 years (SD = 6.8) compared to 16.0 years (SD = 7.6) for patients who did not experience grade 3 or 4 toxicity (p = 0.01 by unpaired t-test). Low-income patients had a higher incidence of grade 3 or 4 toxicity compared to other patients (84% vs. 50%; odds ratio for toxicity for low-income patients = 4.88; 95% CI 2.03 – 11.71; p < 0.001). Patients enrolled in clinical trials also experienced significantly more grade 3 or 4 toxicity than patients treated with trial regimens off study (83% vs. 57%; odds ratio for toxicity for patients on study = 3.64; 95% CI 1.40 – 9.51; p = 0.008). Sex, body mass index (analyzed in tertiles), cumulative chemotherapy dose (analyzed as score and as continuous raw data), chemotherapy dose-intensity (analyzed as score and as continuous raw data), tumor size, tumor site, or metastatic status did not correlate statistically with the incidence of toxicity. Local control modality also did not correlate statistically with toxicity, though only 6 patients in this cohort had combined surgery and radiation as local control, with an 83% incidence of grade 3 or 4 toxicity.

A logistic regression model was constructed to evaluate the independent impact of age, ethnicity, income, and clinical trial status on risk of toxicity (Table 4). Age less than 12 years, family income, and clinical trial participation remained independent predictors of grade 3 or 4 non-hematologic toxicity in this model. Low family income was the strongest

predictor of toxicity (odds ratio 4.97; 95% confidence interval 1.9 – 13.1). Latino ethnicity was not an independent predictor of toxicity. Pelvic tumor site emerged as a new predictor of toxicity not noted on bivariate analyses. No statistical interactions between the included variables were noted.

We performed sensitivity analyses that controlled separately for sex, tumor size, metastatic status, type of local control, and chemotherapy exposure (cumulative dose and dose intensity). With these analyses, point estimates for the odds ratios for the identified independent predictors of toxicity remained approximately stable. In order to account for universally missing data for family income in patients over 21 years of age, multiple imputation was performed to derive estimates of this variable for older patients. This analysis yielded similar results to those obtained without the use of imputed data.

Discussion

This study provides new data on predictors of acute non-hematologic toxicity during upfront chemotherapy in this disease. On bivariate analyses, Latino ethnicity, low income, age less than 12 years at diagnosis, and receipt of upfront therapy on a clinical trial were all associated with increased toxicity in this population. The independent contribution of low income, young age, and clinical trial participation to an increased risk of toxicity was confirmed by multivariate analysis, while pelvic tumor site was also found to be associated with a higher risk of toxicity.

Low family income proved to be the strongest predictor of toxicity in our cohort. An association between low income and increased incidence of toxicity has been demonstrated in only a small number of studies of pediatric acute leukemia [26], other pediatric cancers [27], and in adults with cancer [28]. Association between low income and poor cumulative childhood health in the general population is better established and includes nutritional status, chronic disease, and mental health outcomes [29,30]. While the etiology for this disparity in patients with ES is not clear, other groups have postulated that disparate access to healthcare in lower income populations may result in more advanced presentation of initial disease, advanced presentation at time of treatment complications, delayed recognition of toxicity, and inability to seek care [26,27]. Disparity in cumulative health due to lower income may also play a role. Based on these data, increased vigilance to toxicity and increased supportive care measures are recommended for low-income patients receiving intensive therapy for ES.

On bivariate analysis, Latino patients had higher rates of toxicity. Latino ethnicity approached significance, but was not predictive of toxicity on multivariate analysis. While this finding may reflect confounding by other factors, such as income, it is also possible that the small number of Latino patients in our cohort may have resulted in the loss of statistical significance in the model. Latino ethnicity as a risk factor for toxicity has not been widely identified in the adult or pediatric literature. Two studies demonstrated that Latino patients are less likely to experience myelodysplastic syndrome or AML as a long-term consequence of childhood cancer therapy with alkylating agents [20,22], epipodophyllotoxins, or radiation [20], when compared to white, non-Latino patients. A study of childhood acute leukemias found that Latino patients experienced more acute cardiac toxicity and comparable neuropsychiatric and hematologic toxicity compared to white non-Latino patients [22]. Finally, review of common pediatric cancers suggests that Latino ethnicity may be independently associated with increased toxicity [21]. Our current findings complement previous work demonstrating disparities in overall outcomes in Latino patients with ES and other diseases [28,31,32]. The paucity of studies in this area coupled with the

growing Latino population in the United States suggests a need for additional work focused on this disparity.

Pharmacogenomic differences between Latino and non-Latino patients may also provide an explanation for the observed differences in toxicity based on ethnicity [28]. Specifically, polymorphisms in enzymes of metabolism including UDP glucuronosyltransferase 1A (UGT1A) and N-acetyl transferase (NAT) have been shown to effect metabolism of numerous chemotherapy agents used to treat childhood cancers [21,28,33]. Latinos have a higher expression of NAT24 phenotype and varied expression of UGT1A compared to white, non-Latinos that could account for differences in drug metabolism between the two populations [28].

Additionally, we found that young patients and patients with pelvic primary tumors are at higher risk for chemotherapy related toxicity. The impact of young age as a risk factor for chemotherapy-associated toxicity has been inconclusive in previous work [9]. Potential reasons for increased toxicity in younger patients might include physiologic, pharmacologic, and social etiologies. The increased risk of toxicity in patients with pelvic primary tumors may be due to increased burden of disease, increased risk of metastases, or the increased use of radiation therapy in these patients.

Although these results are derived from a retrospective cohort study, this study is notable for a number of important strengths. As our cohort included both patients enrolled on clinical trials and patients treated according to standard therapy, our results are likely generalizable to general pediatric oncology practice. Since most grade 3 and 4 toxicities require medical evaluation or hospitalization, it is likely that our chart review captured the majority of these events in this cohort. Further, the overall incidence of grade 3 or 4 toxicity in the current cohort was similar to previous reports from cooperative group ES trials [4,34].

While this study provides the most complete data to date regarding predictors of toxicity in ES patients both enrolled in clinical study and treated off study, a number of potential limitations were present. First, in order to develop a sufficiently large cohort we included patients with localized and metastatic disease in the same analysis. Metastatic patients were anticipated to have increased toxicity due to increased disease burden and more aggressive upfront therapy. However, we did not find a difference in the incidence of toxicity between patients with metastatic and localized disease. It is possible that lower grade toxicities are nevertheless more common in patients with metastatic disease. Second, patients enrolled on clinical trials had increased rates of toxicity compared to those treated per clinical trial regimens, but off study. This result may be subject to ascertainment bias due to the study requirements for reporting toxicity, rather than actual increased incidence of toxicity in clinical trial patients. Further, although we did not observe an effect of year of diagnosis on toxicity, documentation of adverse events may have evolved divergently for clinical study patients versus off study patients over time. This possible divergence is unlikely however, as adverse event grading was confirmed in the review and based on primary hospital records when necessary. Also, the rate of clinical trial enrollment over the time period reviewed was similar in this cohort until 2005 when AEWS0031 closed to enrollment. Next, our method to compare cumulative dose and dose-intensity to toxicity may have failed to identify a difference in toxicity based on chemotherapy doses due to mandatory dose reductions for patients with grade 3 and 4 toxicity. Reduced doses would likely affect cumulative dose, dose intensity or both for a given patient. However, preliminary results of Children's Oncology Group protocol AEWS0031 indicate that rates of serious toxicity are not increased with an interval compressed chemotherapy regimen in this population [25]. In addition, our analysis does not include nutrition, distance to treating center, and differences in supportive care measurements among patients. Finally, available records did not allow

adequate analysis of late toxicity or secondary malignancy to assess predictors of late treatment effects. Given the data for late effects in other pediatric cancers, further study is warranted in this disease [20,22].

The results of the current study demonstrate differences in toxicity to upfront chemotherapy for ES patients according to income, ethnicity, age, tumor site, and clinical trial participation. Although the reasons for these differences are unknown, clinicians should be vigilant to potential increased risk for toxicity in younger patients, Latino patients, low-income patients, and patients with pelvic tumors. The majority of toxicities were febrile neutropenia and infection. The frequencies and severity of these toxicities may be reduced or mitigated by better supportive measure and closer observation for higher risk patients. Prevention of toxicity based on supportive care rather than alteration of chemotherapy dosing is particularly emphasized since dose and dose-intensity did not correlate with toxicity. Moreover, previous work has demonstrated that Latino patients have inferior outcomes with this disease [35], further arguing that treatment administration not be compromised for these patients based on the current findings. Further investigation, including detailed pharmacogenomics studies, are needed to understand the etiology of the observed differences in toxicity in these identified patient subgroups.

Acknowledgments

Support: Supported by the Campini Foundation and NIH/NCRR/OD UCSF-CTSI Grant Number KL2 RR024130. The contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

References

1. Esiashvili N, Goodman M, Marcus RB Jr. Changes in incidence and survival of Ewing sarcoma patients over the past 3 decades: Surveillance Epidemiology and End Results data. *Journal of Pediatric Hematology/Oncology*. 2008; 30(6):425–430. [PubMed: 18525458]
2. Gurney, JS,AR.; Bulterys, M. Cancer incidence and survival among children and adolescents: United States SEER program 1975–1995. Bethesda: SEER program, National Cancer Institute; 1999.
3. Balamuth NJ, Womer RB. Ewing's sarcoma. *The Lancet Oncology*. 2010; 11(2):184–192. [PubMed: 20152770]
4. Granowetter L, Womer R, Devidas M, et al. Dose-intensified compared with standard chemotherapy for nonmetastatic Ewing sarcoma family of tumors: a Children's Oncology Group Study. *Journal of Clinical Oncology*. 2009; 27(15):2536–2541. [PubMed: 19349548]
5. Ladenstein R, Potschger U, Le Deley MC, et al. Primary disseminated multifocal Ewing sarcoma: results of the Euro-EWING 99 trial. *Journal of Clinical Oncology*. 2010; 28(20):3284–3291. [PubMed: 20547982]
6. Gupta AA, Pappo A, Saunders N, et al. Clinical outcome of children and adults with localized Ewing sarcoma: impact of chemotherapy dose and timing of local therapy. *Cancer*. 2010; 116(13): 3189–3194. [PubMed: 20564643]
7. Juergens C, Weston C, Lewis I, et al. Safety assessment of intensive induction with vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) in the treatment of Ewing tumors in the EURO-E.W.I.N.G. 99 clinical trial. *Pediatric Blood & Cancer*. 2006; 47(1):22–29. [PubMed: 16572419]
8. Stohr W, Paulides M, Bielack S, et al. Ifosfamide-induced nephrotoxicity in 593 sarcoma patients: A report from the late effects surveillance system. *Pediatr Blood Cancer*. 2007; 48:447–452. [PubMed: 16628552]
9. Skinner R. Nephrotoxicity--what do we know and what don't we know? *Journal of Pediatric Hematology/Oncology*. 2011; 33(2):128–134. [PubMed: 21285904]

10. Jeddi R, Kacem K, Ben Neji H, et al. Predictive factors of all-trans-retinoic acid related complications during induction therapy for acute promyelocytic leukemia. *Hematology*. 2008; 13(3):142–146. [PubMed: 18702871]
11. Lange BJ, Gerbing RB, Feusner J, et al. Mortality in overweight and underweight children with acute myeloid leukemia. *JAMA*. 2005; 293(2):203–211. [PubMed: 15644547]
12. Ruggiero A, Coccia P, Scalzone M, Attina G, Riccardi R. Treatment of childhood sarcoma with irinotecan: bilirubin level as a predictor of gastrointestinal toxicity. *Journal of Chemotherapy*. 2009; 21(6):693–697. [PubMed: 20071295]
13. Aquerreta I, Aldaz A, Giraldez J, Sierrasesumaga L. Pharmacodynamics of high-dose methotrexate in pediatric patients. *The Annals of Pharmacotherapy*. 2002; 36(9):1344–1350. [PubMed: 12196049]
14. Aplenc R, Lange B. Pharmacogenetic determinants of outcome in acute lymphoblastic leukaemia. *British Journal of Haematology*. 2004; 125(4):421–434. [PubMed: 15142113]
15. Barahmani N, Carpentieri S, Li XN, et al. Glutathione S-transferase M1 and T1 polymorphisms may predict adverse effects after therapy in children with medulloblastoma. *Neuro-oncology*. 2009; 11(3):292–300. [PubMed: 18952980]
16. Renbarger JL, McCammack KC, Rouse CE, Hall SD. Effect of race on vincristine-associated neurotoxicity in pediatric acute lymphoblastic leukemia patients. *Pediatric Blood & Cancer*. 2008; 50(4):769–771. [PubMed: 18085684]
17. Metzger ML, Hudson MM, Somes GW, et al. White race as a risk factor for hypothyroidism after treatment for pediatric Hodgkin's lymphoma. *Journal of Clinical Oncology*. 2006; 24(10):1516–1521. [PubMed: 16575001]
18. Trevino LR, Shimasaki N, Yang W, et al. Germline genetic variation in an organic anion transporter polypeptide associated with methotrexate pharmacokinetics and clinical effects. *Journal of Clinical Oncology*. 2009; 27(35):5972–5978. [PubMed: 19901119]
19. Bhatla D, Gerbing RB, Alonzo TA, et al. Cytidine deaminase genotype and toxicity of cytosine arabinoside therapy in children with acute myeloid leukemia. *British Journal of Haematology*. 2009; 144(3):388–394. [PubMed: 19036079]
20. Aguilera DG, Vaklavas C, Tsimberidou AM, Wen S, Medeiros LJ, Corey SJ. Pediatric therapy-related myelodysplastic syndrome/acute myeloid leukemia: the MD Anderson Cancer Center experience. *Journal of Pediatric Hematology/Oncology*. 2009; 31(11):803–811. [PubMed: 19801947]
21. Bhatia S. Disparities in cancer outcomes: lessons learned from children with cancer. *Pediatric Blood & Cancer*. 2011; 56(6):994–1002. [PubMed: 21328525]
22. Haddy TB, Mosher RB, Reaman GH. Late effects in long-term survivors after treatment for childhood acute leukemia. *Clinical Pediatrics*. 2009; 48(6):601–608. [PubMed: 19264722]
23. Worch J, Cyrus J, Goldsby R, Matthay KK, Neuhaus J, DuBois SG. Racial differences in the incidence of mesenchymal tumors associated with EWSR1 translocation. *Cancer Epidemiology, Biomarkers & Prevention*. 2011; 20(3):449–453.
24. Smith MA, Ungerleider RS, Horowitz ME, Simon R. Influence of doxorubicin dose intensity on response and outcome for patients with osteogenic sarcoma and Ewing's sarcoma. *Journal of the National Cancer Institute*. 1991; 83(20):1460–1470. [PubMed: 1833556]
25. Womer RB, West MD, Kralio PS, Dickman PS, Pawel B. Randomized comparison of every-three-week chemotherapy in Ewing sarcoma family tumors (ESFT). *Journal of Clinical Oncology*. 2008; 26(suppl 15):A-10504.
26. Gupta S, Bonilla M, Fuentes SL, et al. Incidence and predictors of treatment-related mortality in paediatric acute leukaemia in El Salvador. *British Journal of Cancer*. 2009; 100(7):1026–1031. [PubMed: 19293804]
27. Hudson MM, Mulrooney DA, Bowers DC, et al. High-risk populations identified in Childhood Cancer Survivor Study investigations: implications for risk-based surveillance. *Journal of Clinical Oncology*. 2009; 27(14):2405–2414. [PubMed: 19289611]
28. Ma BB, Hui EP, Mok TS. Population-based differences in treatment outcome following anticancer drug therapies. *The Lancet Oncology*. 2010; 11(1):75–84. [PubMed: 20129130]

29. Currie J, Lin W. Chipping away at health: More on the relationship between income and child health. *Health Affairs*. 2007; 26(2):331–344. [PubMed: 17339659]
30. Sellstrom E, Bremberg S. The significance of neighbourhood context to child and adolescent health and well-being: a systematic review of multilevel studies. *Scandinavian Journal of Public Health*. 2006; 34(5):544–554. [PubMed: 16990166]
31. Yang JJ, Cheng C, Devidas M, et al. Ancestry and pharmacogenomics of relapse in acute lymphoblastic leukemia. *Nature Genetics*. 2011; 43(3):237–241. [PubMed: 21297632]
32. Worch J, Matthay KK, Neuhaus J, Goldsby R, DuBois SG. Ethnic and racial differences in patients with Ewing sarcoma. *Cancer*. 2010; 116(4):983–988. [PubMed: 20052725]
33. Walker K, Ginsberg G, Hattis D, Johns DO, Guyton KZ, Sonawane B. Genetic polymorphism in N-Acetyltransferase (NAT): Population distribution of NAT1 and NAT2 activity. *Journal of Toxicology and Environmental Health. Part B*. 2009; 12(5–6):440–472.
34. 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. *The New England Journal of Medicine*. 2003; 348(8):694–701. [PubMed: 12594313]
35. Lee J, Hoang BH, Ziogas A, Zell JA. Analysis of prognostic factors in Ewing sarcoma using a population-based cancer registry. *Cancer*. 2010; 116(8):1964–1973. [PubMed: 20151425]

Table 1

Characteristics of 142 patients with ES and available toxicity data

Characteristic	Patients		Characteristic	Patients	
	No.	%		No.	%
Sex			Stage		
Male	89	63	Localized	95	69
Female	53	37	Metastatic	43	31
Ethnicity			Year of Diagnosis		
Latino	39	27	1980–84	2	1
Non-Latino	103	73	1985–89	2	1
			1990–94	12	9
Income (CCS Eligibility)			1995–99	34	24
Eligible	64	53	2000–04	39	28
Ineligible	57	47	2005–10	52	37
Age, years			Chemotherapy Regimen		
<12	47	33	VACA	8	6
12	95	67	VDCIE	122	85
			VIDE	3	2
Primary Site			Investigational/other	10	9
Appendicular	68	49			
Axial	72	51	Clinical Trial Status		
			On Study	35	25
Pelvic	25	18	Not On Study	107	75
Non-pelvic	117	82			
			Cumulative Chemotherapy		
Tissue of Origin			Low	0	0
Bone	118	84	Normal	39	34
Soft Tissue	22	16	High	76	66
Tumor Size, cm			Chemotherapy Dose Intensity		
6	23	20	Low	58	53
>6	90	80	Normal	32	29
			High	19	18

Characteristic	Patients		Characteristic		Patients	
	No.	%			No.	%
Body Mass Index						
Bottom Tertile	32	33	Type Local Control			
Middle Tertile	32	33	Surgery		77	58
Top Tertile	33	34	Radiation		49	37
			Surgery and Radiation		6	5

VACA = Vincristine, adriamycin, cyclophosphamide, actinomycin D; VDCIE = Vincristine, doxorubicin, cyclophosphamide, ifosfamide, etoposide; VIDE = Vincristine, ifosfamide, doxorubicin, etoposide

Table 2

Treatment Related Grade 3 and 4 Events

Adverse Event	No. Treated On Study (%)		No. Treated Off Study (%)	
	Grade 3	Grade 4	Grade 3	Grade 4
Febrile Neutropenia	23 (66%)	1 (3%)	47 (44%)	3 (2%)
Infection	15 (43%)		27 (25%)	3 (2%)
Mucositis	2 (6%)		8 (7%)	
Vomiting	4 (11%)		4 (4%)	
Anorexia	1 (3%)		2 (2%)	
Hyponatremia			2 (2%)	
Ovarian Failure			2 (2%)	
Peripheral Neuropathy	1 (3%)		1 (1%)	
Rash	1 (3%)		1 (1%)	
Weight Loss	2 (6%)			
Pulmonary Embolism		1 (3%)	1 (1%)	
Cellulitis	1 (3%)			
DVT			1 (1%)	
Diarrhea	1 (3%)			
Encephalopathy			1 (1%)	
Hypocalcemia			1 (1%)	
Liver Failure			1 (1%)	
Urinary Retention	1 (3%)			
Vasovagal Episode			1 (1%)	

Table 3

Bivariate analysis of potential predictors of grade 3 and 4 toxicity

Characteristic	Grade 3 / 4 Toxicity			Grade 3 / 4 Toxicity		
	No.	%	p	Characteristic	No.	% p
Sex				Tumor Size, cm		
Male	53	60	0.280	6	14	61 0.814
Female	37	70		>6	57	63
Ethnicity				Tissue of Origin		
Latino	32	82	0.006	Bone	74	63 0.470
Non-Latino	58	56		Soft Tissue	16	73
Body Mass Index				Stage		
Bottom Tertile	23	72	0.439	Localized	62	65 1.000
Middle Tertile	17	56		Metastatic	28	65
Top Tertile	20	61		Clinical Trial Status		
Household Income				On Study	29	83 0.008
Low	48	84	0.001	Not On Study	61	57
Standard	32	50		Cumulative Chemotherapy		0.675
Age at Diagnosis				Low	0	0
<12 years	37	79	0.009	Normal	28	72
12 years	53	59		High	51	67
Primary Site				Chemotherapy Dose Intensity		0.618
Appendicular	50	69	0.219	Low	42	72
Axial	40	59		Normal	20	63
Primary Site				High	13	68
Pelvic	19	76	0.175	Type Local Control		0.315
Non-pelvic	71	61		Surgery	53	69
				Radiation	28	57
				Surgery and Radiation	5	83

Table 4

Multivariate Analysis of Grade 3 and 4 Non-Hematologic Toxicity

	Odds Ratio	95% CI	p
Household Income			
Low income	4.97	1.88–13.13	0.001
Standard income	Reference		
Tumor Site			
Pelvic	3.88	1.17–12.88	0.027
Other	Reference		
Clinical Trial Status			
On Study	3.67	1.24–10.88	0.019
Not on study	Reference		
Age at Diagnosis			
<12 years	2.79	1.04–7.45	0.041
12 years	Reference		
Ethnicity			
Latino	2.55	0.90–7.20	0.078
Non-Latino	Reference		