Cost Minimization Analysis of Two Treatment Regimens for Low-Risk Rhabdomyosarcoma in Children: A Report From the Children's Oncology Group

Heidi Russell, MD,^{1,2*} J. Michael Swint, PhD,^{2,3} Lincy Lal, PharmD, PhD,² Jane Meza, PhD,⁴ David Walterhouse, MD,⁵ Douglas S. Hawkins, MD,⁶ and M. Fatih Okcu, MD, MPH¹

Background. Recent Children's Oncology Group trials for low-risk rhabdomyosarcoma attempted to reduce therapy while maintaining excellent outcomes. D9602 delivered 45 weeks of outpatient vincristine and dactinomycin (VA) for patients in Subgroup A. ARST0331 reduced the duration of therapy to 22 weeks but added four doses of cyclophosphamide to VA for patients in Subset 1. Failure-free survival was similar. We undertook a cost minimization comparison to help guide future decision-making. **Procedure.** Addressing the costs of treatment from the healthcare perspective we modeled a simple decision-analytic model from aggregate clinical trial data. Medical care inputs and probabilities were estimated from trial reports and focused chart review. Costs of radiation, surgery and off-therapy surveillance were excluded. Unit costs were obtained from literature and national reimbursement and inpatient utilization databases and converted to 2012 US dollars.

Model uncertainty was assessed with first-order sensitivity analysis. **Results.** Direct medical costs were \$46,393 for D9602 and \$43,261 for ARST0331 respectively, making ARST0331 the less costly strategy. Dactinomycin contributed the most to D9602 total costs but varied with age (42–69%). Chemotherapy administration costs accounted for the largest proportion of ARST0331 total costs (39–57%). ARST0331 incurred fewer costs than D9602 under most alternative distributive models and alternative clinical practice assumptions. **Conclusions.** Cost analysis suggests that ARST0331 may incur fewer costs than D9602 from the healthcare system's perspective. Attention to the services driving the costs provides directions for future efficiency improvements. Future studies should prospectively consider the patient and family's perspective. *Pediatr Blood Cancer* 2014;61:970–976. © 2014 Wiley Periodicals, Inc.

Key words: childhood cancer; cost analysis; rhabdomyosarcoma

INTRODUCTION

Sequential cooperative-group prospective clinical trials have improved outcomes for children with rhabdomyosarcoma (RMS) [1]. Since the 1970's the Intergroup Rhabdomyosarcoma Study Group (IRSG) and then the Children's Oncology Group (COG) have established the role of chemotherapy in RMS, the importance of local control with radiation therapy and surgery and risk stratification for treatment based on tumor site, stage, surgical group, and histology. Localized embryonal RMS arising in favorable sites or unfavorable sites that have been grossly resected before beginning chemotherapy have emerged as having a low-risk of treatment failure [1,2]. Consequently the two most recent cooperative group clinical trials for low-risk RMS, COG D9602, and COG ARST0331, attempted to reduce chemotherapy exposure and treatment burden while maintaining high failure-free survival (FFS) rates.

D9602 enrolled 246 patients from 1997 until 2004 onto treatment according to Subgroup A for the lowest-risk patients. These children had embryonal, botryoid, spindle cell, or embryonal ectomesenchymoma histology in stage 1 groups I/IIA, group III orbit, or stage 2 group I [3]. Patients received vincristine (VCR) and dactinomycin (DACT) (VA) for 45 weeks, a treatment designed for delivery in the outpatient setting. FFS rates on D9602 were similar to previous regimens using more intensive therapy. At 3 years the estimated FFS for Subgroup A was 89% (95% CI: 84–93%) [3] and these results were maintained as the cohort matured. ARST0331 subsequently decreased treatment duration from 45 to 22 weeks but added four doses of cyclophosphamide (CPM) in combination with VA (VAC) in the first 12 weeks requiring more intensive supportive measures. Both regimens included similar radiotherapy and surgical guidelines. ARST0331 also included patients with stage 1 group IIB/C or stage 2 group II tumors in the lowest risk group, Subset 1, because these patients had comparable FFS rates with the lowest risk group on earlier IRSG trials. From 2004 until 2011, 271 children enrolled onto Subset 1 of this study. Early analysis

demonstrated a similar pattern of successful treatment: the 2 year estimated FFS was 88% (95% CI: 82%, 92%) [4]. Treatment failures on D9602 were most common in the first 2 years from diagnosis [3], assuming that ARST0331 continues to follow this trend FFS at 3 years should not change appreciably.

Given the similar FFS of D9602 and ARST0331, the preferred treatment approach is not clear. While these studies may have similar successful FFS outcomes they use different types of health

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

¹Texas Children's Cancer and Hematology Centers, Baylor College of Medicine, Houston, Texas; ²University of Texas School of Public Health, Division of Management, Policy and Community Health, Houston, Texas; ³University of Texas School of Medicine, Center for Clinical Research and Evidence-Based Medicine, Houston, Texas; ⁴University of Nebraska Medical Center College of Public Health, University of Nebraska Medical Center, Omaha, Nebraska; ⁵Ann & Robert H Lurie Children's Hospital of Chicago, Division of Hematology/Oncology/Stem Cell Transplant, Chicago, Illinois; ⁶Seattle Children's Hospital, Fred Hutchinson Cancer Research Center, University of Washington, Department of Pediatrics, Seattle, Washington

Grant sponsor: UTHealth Innovation Cancer Prevention Research Postdoctoral Fellowship, Cancer Prevention and Research Institute of Texas; Grant number: RP101503r

Conflict of Interest: Nothing to report.

The results of this study were presented in abstract form at the Third Annual Meeting of the Cancer Prevention and Research Institute of Texas, October 24–26, 2012.

*Correspondence to: Heidi Russell, Texas Children's Cancer and Hematology Centers, 6701 Fannin, CCC 1510.00, Houston, TX 77030. E-mail: hvrussel@txch.org

Received 15 July 2013; Accepted 16 December 2013

care resources and impact the patient and his/her family differently. Monetary valuing strategies may provide additional data to consider when choosing between treatment options. To that end we performed a cost minimization analysis to compare D9602 Subgroup A to ARST0331 Subset 1 from the perspective of the health care system.

METHODS

Patient Population

COG trials D9602 and ARST0331 were the primary data sources for this analysis. Both studies completed enrollment at the time of this cost analysis. Demographic data were used in aggregate from these trials. ARST0331 did not collect data regarding common toxicities; therefore retrospective chart reviews were performed to supplement this information. All patients who received at least four courses of chemotherapy on ARST0331 or its equivalent (treat-according-to) at Texas Children's Hospital after September 1, 2004 until present were identified from existing databases. The medical records of these patients were examined for transfusions, admissions for possible or documented infections, and neurologic toxicities requiring intervention beyond reducing the dose of vincristine. Use of myeloid growth factor support was also captured for each cycle of CTM received. The 13 subjects identified in this review are presented in Table SI. The Baylor College of Medicine Institutional Review Board approved this research.

Decision Analytic Model

A cost minimization analysis was performed because the primary outcome of the two treatment regimens, FFS, was similar.

A simple decision-analytic model was constructed in TreeAge Pro 2012 (Williamstown, MA) (Fig. 1) using D9602 Subgroup A as the base case and ARST0331 Subset 1 as the alternative case from the perspective of the healthcare system. Because weight/body surface area-based chemotherapy dosing varies by age on these regimens (Table I), the decision tree included branches for each major dosing schedule. We assumed patients received magnetic resonance imaging (MRI) for imaging of head/neck or limb tumors and computerized tomography (CT) for body tumors. We also assumed that patients 7 years old or younger were sedated for MRI.

Inputs

All interventions prescribed during active treatment by the clinical trials were included except costs of surgery and radiation therapy. These modalities were excluded because recommendations were similar between D9602 and ARST0331 and highly dependent on the tumor location. We also excluded studies performed specifically for verification of eligibility onto the clinical trials and interventions performed on both regimens (example central venous catheter placement). To determine pharmaceutical dosing, weight, and body surface area were estimated for a median aged child of each age range using established growth curves [5]. Protocol required or recommended medications aimed to minimize toxicities, laboratory studies, and imaging were included in the estimations of cost. Guidelines for myeloid growth factor support were provided for ARST0331, but utilization of growth factors was not collected for the study report. We estimated 1 cycle of filgrastim (10 daily injections) for each hypothetical patient based on the utilization of the 10 patients reviewed who were enrolled in ARST0331. We assumed CPM would be given in a 1-day

Fig. 1. Decision tree for comparing chemotherapy regimens for low-risk rhabdomyosarcoma. Chemotherapy dosing on each regimen was determined by patient age. Tumor imaging with magnetic resonance imaging (MRI) or computerized tomography (CT) was assumed according to primary tumor location. All patients 7 years old or younger were assumed to require sedation for MRI.

TABLE I. Chemotherapy and Supportive Drug Dose Schedule by Age

	D9602	ARST0331	Dose
VCR (IV)	Infants <1 year: 0.025 mg/kg/dose Children 1–2.99 years: 0.05 mg/kg/dose Children ≥3 years: 1.5 mg/m ² /dose		0.2 mg/dose 0.6 mg/dose 1.35 mg/dose
DACT (IV)	Infants <1 year: 0.025 mg/kg/dose Children ≥1 year: 0.045 mg/kg/dose		0.2 mg/dose 1.13 mg/dose
CPM (IV)	NA	Infants and children <3 years: 40 mg/kg/dose Children ≥3 years: 1,200 mg/m ² /dose	320–488 mg/dose 1,080 mg/dose
MESNA (IV)	NA	60% of CPM dose	
Filgrastim (SQ)	NA	5 mcg/kg/day if previous complications	

VCR, vincristine; DACT, actinomycin D; CPM, cyclophosphamide; IV, intravenous; SQ, subcutaneous.

hospitalization and all other chemotherapy would be given as an outpatient.

Chemotherapy incurs well-described toxicities. Many of these are not associated with a medical intervention (e.g., alopecia). We identified grade 3 or 4 toxicities during or within 2 months of completion of chemotherapy likely to be associated with a medical intervention (infection, anemia, thrombocytopenia, neuropathy). Severe but rare toxicities such as hepatopathy were excluded because of a lack of a standard treatment or capture of treatments performed making an estimate unreliable. The probability of toxicities for D9602 was derived from the reported incidence on the trial. Likelihoods of toxicities for ARST0331 were derived from the toxicities identified by chart review and supported by findings in the published literature. Treatment plans for patients with relapsed disease were not included in this analysis. Probable age distribution of hypothetical patients was determined by the actual distribution of patients enrolled on these studies. Differences in primary tumor location and outcome by age were supported by additional literature.

Costs

Costs for each input unit were obtained from national databases and inflated to 2012 US dollars (US\$) using the Consumer Price Index [6]. No cost discounting was applied because treatments lasted <1 year. Pharmaceutical costs were estimated by Average Wholesale Price (AWP) [7] and rounded to the next vial size except when noted in Table II. Costs of laboratory tests, imaging studies, outpatient chemotherapy administration and physician services were estimated from Center for Medicaid and Medicare Services (CMS) reimbursement rates for 2012 [8]. Inpatient hospitalization costs for chemotherapy were estimated from the Healthcare Cost Utilization Project (H-CUP) Kids Inpatient Database (KID) from 2003, 2006, and 2009. Cost-to-charge ratios provided by H-CUP were applied to convert total admission charges to costs. Specific admissions included in estimating inpatient costs were defined as associated with a Clinical Classification Software [9] code for cancer diagnoses, 11 and 34, ICD-9 procedure code 99.25, and lasting 1 day.

Sensitivity Analysis

We conducted several sensitivity analyses to explore the impact of changes in model scenarios. Tornado analyses were performed on cost and likelihood ranges to identify key variables for further

first order sensitivity analysis. First order sensitivity analysis utilized ranges of 0–1 for likelihood and the minimum and maximum mean values for the costs. Second order sensitivity analysis utilized the gamma distribution for costs and the beta distribution for likelihood. One thousand 1st order Monte-Carlo micro-simulations were used to generate cost estimates and selection probabilities.

Alternative delivery scenarios were developed to account for clinical variations occurring in practice. An alternative scenario wherein CPM was delivered in an outpatient setting assumed that all chemotherapy, hydration, and supportive medications would be given within a standard working day (i.e., 8 hours). A second alternative scenario was developed using myeloid growth factor following each CPM dose, that is, primary prophylaxis of neutropenia-related infections. This model assumed that single dose PEG-filgrastim would be used for prophylaxis rather than daily dose filgrastim to minimize the number of needle-sticks in the pediatric patient.

RESULTS

Base Case Analysis

The base-case analysis was performed using the previously stated assumptions, and likelihoods and costs from Table II. In this analysis from the healthcare perspective, the direct medical costs of D9602 Subgroup A were \$46,393 while the costs for ARST0331 Subset 1 were \$43,261. Therefore ARST0331 was the least costly strategy by \$3,132. ARST0331 was chosen in 90% of Monte-Carlo micro-simulations.

Sensitivity Analysis

We compared the relative importance of each branch of the decision tree by Tornado diagrams individually varying the variable costs and likelihoods (Fig. 2). Increasing the likelihood of patients being <1-year-old or 1–3 years old had the greatest impact on the estimated cost per patient as shown in the range of values in the top four bars of Figure 2A. Varying costs alone while holding likelihoods of events such as age distribution or having a toxicity stable resulted in a lesser impact on the estimated costs and then only in the older patients on ARST0331 (Fig. 2B). When estimated costs per patient and first order sensitivity analysis were performed for each age range separately (Table III), estimated costs for infants were \$14,000 to \$22,650 lower than for patients over 3 years old.

TABLE II. Input Parameters

Model input variable	Estimate	Reference
Probability (likelihood)		
D9602 Age		
<1 yo	0.07	[21]
1–3 yo	0.14	[21]
>3 yo	0.79	[21]
ARST0331 Age		
<1 yo	0.07	[22]
1–3 yo	0.15	[22]
>3 yo	0.78	[22]
Primary tumor imaging with MRI (vs. CT scan)	0.42	[3,21–23]
if patient is <1 yo		
Primary tumor imaging with MRI (vs. CT scan)	0.52	[3,21,22]
if patient is ≥1 yo		
Grade 3 or 4 toxicity		
D9602	0.73	[3,21]
ARST0331	0.64	[24,25] ^b
Costs (2012 US\$)		
Anti-tumor drugs		
Vincristine 1 mg	5.84	AWP [7]
Dactinomycin 0.5 mg	707	AWP [7]
Cyclophosphamide 500 mg	147	AWP [7]
Supportive drugs		
MESNA 1,000 mg	61	AWP [7]
Filgrastim 300 mcg ^a	338	AWP [7]
Filgrastim 480 mcg ^a	539	AWP [7]
Depo-filgrastim 6 mg	4,340	AWP [7]
Ondansetron 10 mg	38.52	AWP [7]
Bactrim 400/80 mg	0.66	AWP [7]
Labs		
CBC d/p	9.11	CMS [26], HCPCS code 85025
Creatinine	7.26	CMS [26], HCPCS code 82565
SGPT	7.50	CMS [26], HCPCS code 84460
SGOT	15.88	CMS [26], HCPCS code 84450
Bilirubin	7.10	CMS [26], HCPCS code 82247
Lytes	9.94	CMS [26], HCPCS code 80051
Ca/Phos	17.76	CMS [26], HCPCS code 82310, 84060
Urinalysis	3.04	CMS [26], HCPCS code 81005
Imaging studies		
MRI	723 (range 629–795)	CMS [8], ^c CPT codes 70543, 70553
CT body	389 (range 338–428)	CMS [8], ^c CPT code 72194
CT chest without contrast	258	CMS, CPT code 71250
Sedation for MRI	510 (range 460–561)	[27]
CXR	30–33	CMS [8], ^c CPT code 71010–71035
Bone scan	282 (range 245–310)	CMS [8], ^c CPT code 78306
Administrative		
Inpatient hospitalization—CPM	3,693 (range 1,918–4,657)	Kids Inpatient Database 2003–2009
Outpatient VAC	553 (range 329–691)	CMS [8], ^c CPT codes 96411, 96413, 96375, 96361
Outpatient nursing costs—VCR only	121 (range 106–151)	CMS [8], ^c CPT code 96409
Outpatient nursing costs—VCR + DACT	214 (range 186–268)	CMS [8], ^c CPT codes 96409, 96411, 96375
Outpatient nursing costs—DACT only	146 (range 127–183)	CMS [8], ^c CPT codes 96409, 96375
Physician services	84 (range 73–105)	CMS [8], ^c CPT 99214
Toxicity		
Red blood cells 1 unit, leuko-reduced, irradiated	288	CMS [8], code P9040
Platelet 1 unit, leuko-reduced, irradiated	110	CMS [8], code P9031
Infection	6,125	[28]
Neuropathy-physical therapy	140	CMS [8], CPT code 97112 ^d

CPM, cyclophosphamide; VCR, vincristine; DACT, dactinomycin; VAC, vincristine, actinomycin, and dactinomycin; MRI, magnetic resonance imaging; CT, computerized tomography. ^aAssumed 1 cycle of filgrastim (10 daily injections) per ARST0331 patient. ^bLimited chart reviews. ^cUsed facility fees limiting charge amount for Houston, TX. ^dAssumed weekly physical therapy for 4 weeks.

Fig. 2. Tornado analysis of univariate effects of likelihood (A) and cost (B) variation on expected value (EV). CT, branch including computerized tomography; MRI, branch including magnetic resonance imaging; Tox, branch including toxicity.

D9602 also became the favored regimen for infants in Monte Carlo micro-simulations.

Inputs were plotted by age (Fig. 3) to understand how age impacts costs. DACT, dosed by age and weight, contributed 42–69% of the total cost of D9602 but only 18–38% of ARST0331's total costs. Administrative costs assigned to routine physician visits and costs of delivering chemotherapy did not change with age in this model. Administrative costs accounted for 39–57% of ARST0331's total costs, driven primarily by costs of inpatient admissions totaling \$14,772 (83%). Outpatient chemotherapy delivery costs, estimated at \$6,066, made up 82% of the administrative costs for D9602. However these costs represented only 15–27% of D9602's total costs.

The costs of ARST0331 remained lower than those of D9602 in alternative models (Table III). We tested the decision model using different cost and likelihood models using first and second order sensitivity analyses. Costs modeled under the gamma distribution neared equivalence. Our original assumptions potentially underestimate the toxicities associated with ARST0331, therefore we estimated the costs if both regimens had the higher toxicity rates documented on D9602. In a second case we reversed probabilities between studies. ARST0331 remained the least costly strategy in both cases.

Costs of ARST0331 changed dramatically in alternative clinical scenarios. Changing delivery of CPM on ARST0331 to the outpatient setting decreased the direct medical costs of ARST0331 by \$12,630 thereby increasing the difference in costs between the two regimens. The addition of primary prophylactic myeloid growth factor after CPM increased the costs of ARST0331 by nearly \$16,000. In this scenario D9602 became the least costly regimen.

DISCUSSION

In this report we have considered the costs of two treatments for low-risk RMS, a childhood cancer with excellent FFS. Both treatment regimens were developed with the goal to maintain survival while decreasing exposure to toxic agents. This analysis suggests that the more recent regimen, ARST0331, incurs fewer direct medical costs than the previous regimen, D9602, by \$3,132 while maintaining similar FFS at 3 years. This incremental cost savings per patient is affected by factors such as the age of the patient, the location of treatment and the use of myeloid growth factors.

DACT was the predominant cost driver of treatment on D9602. Because chemotherapy dosing for both regimens was based on

TABLE III. Alternative Case Scenarios

Parameter	Estimated cost per patient (2012 US\$)		Cost difference (2012 US\$)	1st Order Monte Carlo
	D9602	ARST0331		
All potential patients (base case)	46,393	43,261	3,132	90% in favor of ARST0331
All Patients <1 year old	26,802	31,558	–4,756	100% in favor of D9602
All patients 1–3 years old	38,724	37,497	1,227	87% in favor of ARST0331
All patients >3 years old to adult	49,452	45,407	4,045	100% in favor of ARST0331
Cost model, gamma distribution	47,281	44,848	2,433	88% in favor of ARST0331
Probability model, beta distribution	46,426	43,261	3,165	91% in favor of ARST0331
Assume ARST0331 toxicity likelihood similar to D9602	46,393	44,304	2,089	86% in favor of ARST0331
Exchange toxicity likelihood	45,344	44,304	1,040	80% in favor of ARST0331
Administer VAC in outpatient setting	46,393	30,641	15,752	100% in favor of ARST0331
Use prophylactic myeloid growth factors after VAC	46,393	59,216	–12,823	100% in favor of D9602

Fig. 3. Components of total cost of each regimen. ■ Administrative costs including inpatient hospital costs, outpatient nursing, physician visits. □ Other non-pharmaceutical costs including laboratory, diagnostic imaging, toxicity costs. □ Costs of all other pharmaceuticals including chemotherapy and supportive agents. ■ Costs of dactinomycin.

patient age and size, the component of cost attributable to DACT was greater for older patients. Although ARST0331 also included DACT, patients on this regimen received 50% fewer doses. Costs for ARST0331 were dominated by administrative costs of delivering CPM in the hospital.

This evaluation included costs associated with chemotherapy, the component of treatment for low risk RMS that differed between D9602 and ARST0331. The total costs of treating a child with low-risk RMS will be greater than the estimates presented in this study because we excluded treatment and follow-up costs that were similar between studies or too speculative to allow a reasonable estimate. Surveillance after completion of therapy was similar for both studies and, therefore, not included in this evaluation. We excluded the costs of surgery or radiation therapy because local control is individualized [10] and the guidelines did not change between treatments. We also excluded costs of treatment for recurrent disease, a choice influenced by a lack of an established treatment for recurrent low-risk RMS. Relapse rates and overall survival rates were similar for both studies leading to an assumption that the variation in costs of salvage treatments would be similar for both studies.

We relied on data collected on D9602 and ARST0331 to model our hypothetical patient population and outcomes. We chose a cost minimization model limited to the time of treatment because FFS for both treatment regimens were similar. The structure of patient data collection for these trials also supported a simple cost minimization model over more complicated models. ARST0331, in particular, limited its capture of previously well described toxicities in association with these chemotherapies. Our review of toxicities at a single institution suggested a lower toxicity rate on ARST0331 than on D9602, an unexpected finding following the addition of CPM. Exposure to therapy was twice as long on D9602 as on ARST0331 allowing a longer time to accumulate toxicities. Indeed, the likelihood of a toxicity of interest occurring during the first 24 weeks of D9602 was 0.53. Furthermore when the rates were tested in sensitivity analyses toxicities remained a minor component of costs. An analysis considering costs per life year saved may

be more appropriate in the future if FFS on ARST0331 were to diverge from that of D9602, however the likelihood of this occurring is low. A future study could also include the costs of long-term effects of chemotherapy such as infertility [11,12] if rates differ between regimens.

A small subset of patients were included on ARST0331 Subset 1 who would not have been eligible for D9602, Subgroup A. The change in tumor risk classification was based on a superior outcome on earlier IRSG trials. Preliminarily the outcome for this group of patients on ARST0331 appears no different than outcome for other patients on Subset 1.

The effects of alternative scenarios on differentials in costs suggest future approaches for decreasing costs of treatment. Changing delivery of CPM on ARST0331 to the outpatient setting decreased the direct medical costs of ARST0331. Inpatient CPM delivery represents the most conservative interpretation of the protocol supportive care guidelines for prevention of CPM-induced hemorrhagic cystitis: 24 hours of post-hydration and three individual doses or a 9-hour continuous infusion of MESNA. Hemorrhagic cystitis is a frequent and potentially life-threatening consequence from CPM given during high-dose chemotherapy and stem cell rescue [13], but is less common in moderate doses such as those used in ARST0331. Multiple supportive guidelines for hydration and MESNA delivery exist [14] without empirical evidence for one over another. Some institutions are delivering CPM in the outpatient setting using higher IV infusion rates (personal communication D. Hawkins, doug.hawkins@seattlechildrens.org). We did not vary our risk of hemorrhagic cystitis in this alternative model because of the low incidence despite a myriad of hydration and MESNA guidelines and evidence of safety in outpatient delivery of ifosfamide, an alkylating agent with greater risk of hemorrhagic-cystitis [15]. Increased rates of hemorrhagic cystitis would increase the costs of outpatient CPM, decreasing the cost savings. This alternative scenario illustrates the importance of supportive care delivery as a potential source of cost containment for future investigation.

The second alternative scenario, prophylactic myeloid growth factor, raised the estimated cost of ARST0331 by \$16,000. Growth factors allow patients to receive a chemotherapy dose intensity and prevent readmissions for infection. The introduction of PEG-filgrastim and evidence that count recovery is similar to daily dosing [16] has been especially welcome in pediatric oncology because of the quality of life issues associated with caregivers giving daily injections to a child. Some institutions incorporated growth factors on this regimen under the belief that prevention of an infection would be worth the additional single injection (Supplemental Table and personal communication D. Hawkins, doug.hawkins@seattlechildrens.org). The American Society of Clinical Oncology recently listed primary-prophylactic filgrastim for adult chemotherapy regimens with under 20% risk of infections as one way to decrease minimal-efficacy healthcare [17]. In our review the rate of infection was only 9%, but the sample size was small. Throughout our analysis we identified the weight-based dose of pharmaceuticals but then assumed the cost of the nearest vial size. For filgrastim we relaxed that assumption so that a vial would be used on two consecutive days. Because PEG-filgrastim is dosed once, we applied the original assumption and used the vial as cost. Under these assumptions the cost of a 10 day course of filgrastim for a child under 30 kg would be \$1,405, and a 30–60 kg child would be \$2,810 whereas the cost for PEG-filgrastim would be

\$4,340 regardless of the patient's size. This analysis should not be interpreted as a formal cost-effectiveness analysis of growth factors in low-risk RMS treatment regimens. Rather it supports the effect of age and size on cost of delivering chemotherapy in the pediatric setting and the importance of care delivery on the costs of the treatment.

Ideally this analysis would have included the costs incurred by families. Families of children with cancer bear an enormous financial burden including out-of-pocket medical expenses, loss of wages [18], and increased living expenses (travel to and from medical facilities, food and possibly lodging, care of other children) [19]. Neither family cost nor utility associated with treatment were captured prospectively on either study. We were able to model direct medical costs from national reimbursement databases and aggregated data from the clinical trials, however, similar information for patient costs is limited. While monetary units could be estimated, they would be extremely speculative. Prospective collection of family related costs and quality of life could enhance the choice of the treatments we recommend. In light of the differences in direct medical costs associated with the patient's age, we wonder if age would also influence the family's costs. Previous surveys of families suggest that one adult, usually the mother, limits work outside the home during chemotherapy [20]. The extent may be influenced by the demands of treatment (frequency of treatment, follow-up and risks of toxicities) as well as by the degree of social isolation, for example, keeping a child from school or day care.

In summary, although ARST0331 incurred fewer direct medical costs in most scenarios, the incremental cost savings was small and D9602 was favored for infants and if prophylactic hematopoietic growth factors were included with ARST0331. Age and weight/body surface area-based dosing can influence the total medical costs and should be considered in future cost analyses of childhood cancer treatments. Changes in care delivery could decrease the costs even more. Similarities in total costs suggest the choice between treatments can be influenced by specifics of the institution as well as the needs of the family. Prospective inclusion of family costs and quality of life on future dose-deintensification studies could provide invaluable information.

ACKNOWLEDGMENTS

This work was supported by the UTHealth Innovation for Cancer Prevention Research Post-doctoral Fellowship, The University of Texas School of Public Health—Cancer Prevention and Research Institute of Texas grant # RP101503. The content is solely the responsibility of the authors and does not necessarily

represent the official views of the Cancer Prevention and Research Institute of Texas.

REFERENCES

- Malempati S, Hawkins DS. Rhabdomyosarcoma: Review of the Children's Oncology Group (COG) Soft-Tissue Sarcoma Committee experience and rationale for current COG studies. *Pediatr Blood Cancer* 2012;59:5–10.
- Meza JL, Anderson J, Pappo AS, et al. Analysis of prognostic factors in patients with nonmetastatic rhabdomyosarcoma treated on intergroup rhabdomyosarcoma studies III and IV: The Children's Oncology Group. *J Clin Oncol* 2006;24:3844–3851.
- Raney RB, Walterhouse DO, Meza JL, et al. Results of the Intergroup Rhabdomyosarcoma Study Group 9602; protocol, using vincristine, and dactinomycin with or without cyclophosphamide and radiation therapy, for newly diagnosed patients with low-risk embryonal rhabdomyosarcoma: A report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. *J Clin Oncol* 2011;29:1312–1318.
- Walterhouse DO, Pappo AS, Meza J, et al. Shorter duration therapy that includes vincristine (V), dactinomycin (A), and lower doses of cyclophosphamide (C) with or without radiation therapy for patients with newly diagnosed low-risk embryonal rhabdomyosarcoma (ERMS): A report from the Children's Oncology Group (COG). *J Clin Oncol* (Meeting Abstracts) 2011;29suppl:9516.
- Centers for Disease Control and Prevention. Clinical Growth Charts. http://www.cdc.gov/growthcharts/clinical_charts.htm. Published 2009. Accessed January 6, 2012.
- Bureau of Labor Statistics. Consumer Price Index. United States Department of Labor. <http://www.bls.gov/cpi>. Published 2012. Accessed May 2012.
- Micromedex 2.0. mobileMicromedex. Thomson Reuters. <http://www.library.tmc.edu>. Published 2012. Accessed March 2012.
- Center for Medicaid and Medicare Services. Physician Fee Schedule Search. <http://www.cms.gov/apps/physician-fee-schedule/search/search-criteria.aspx>. Published 2012. Accessed April 2012.
- Elixhauser A, Steiner C, Palmer L. Clinical Classifications Software (CCS), 2004; U.S. Agency for Healthcare Research and Quality; 2004.
- Stevens M. Treatment for childhood rhabdomyosarcoma: The cost of cure. *Lancet Oncol* 2005;6:77–84.
- Katz P, Showstack J, Smith JF, et al. Costs of infertility treatment: Results from an 18-month prospective cohort study. *Fertil Steril* 2011;95:915–921.
- Wu AK, Elliott P, Katz PP, et al. Time costs of fertility care: The hidden hardship of building a family. *Fertil Steril* 2013;99:2025–2030.
- West NJ. Prevention and treatment of hemorrhagic cystitis. *Pharmacotherapy* 1997;17:696–706.
- Sievers TD, Lagan MA, Bartel SB, et al. Variation in administration of cyclophosphamide and mesna in the treatment of childhood malignancies. *J Pediatr Oncol Nurs* 2001;18:37–45.
- Meazza C, Bisogno G, Casanova M, et al. Full-dose ifosfamide can be safely administered to outpatients. *Pediatr Blood Cancer* 2008;50:375–378.
- Spunt SL, Irving H, Frost J, et al. Phase II, randomized, open-label study of pegfilgrastim-supported VDC/IE chemotherapy in pediatric sarcoma patients. *J Clin Oncol* 2010;28:1329–1336.
- Schnipper LE, Smith TJ, Raghavan D, et al. American Society of Clinical Oncology identifies five key opportunities to improve care and reduce costs: the top five list for oncology. *J Clin Oncol* 2012;30:1715–1724.
- Tsimicalis A, Stevens B, Ungar WJ, et al. Determining the costs of families' support networks following a child's cancer diagnosis. *Cancer Nurs* 2012;36:E8–E19.
- Tsimicalis A, Stevens B, Ungar WJ, et al. A mixed method approach to describe the out-of-pocket expenses incurred by families of children with cancer. *Pediatr Blood Cancer* 2012;60:438–445.
- Limburg H, Shaw AK, McBride ML. Impact of childhood cancer on parental employment and sources of income: A Canadian pilot study. *Pediatr Blood Cancer* 2008;51:93–98.
- Raney RB, Walterhouse DO, Meza JL. Final Progress Report: Actinomycin D and Vincristine with or without CPM or RT, for newly diagnosed patients with low-risk embryonal/botryoid rhabdomyosarcoma: IRS-V Protocol, Children's Oncology Group; 2006. p 27.
- Walterhouse DO, Meza J. Study progress report: ARST0331 Vincristine, dactinomycin and lower doses of cyclophosphamide with or without radiation therapy for patients with newly diagnosed low-risk embryonal/botryoid/spindle cell rhabdomyosarcoma. Children's Oncology Group; 2011. p 13.
- Malempati S, Rodeberg DA, Donaldson SS, et al. Rhabdomyosarcoma in infants younger than 1 year: a report from the Children's Oncology Group. *Cancer* 2011;117:3493–3501.
- Pratt CB, Pappo AS, Gieser P, et al. Role of adjuvant chemotherapy in the treatment of surgically resected pediatric nonrhabdomyosarcomatous soft tissue sarcomas: A Pediatric Oncology Group Study. *J Clin Oncol* 1999;17:1219–1226.
- Pritchard J, Imeson J, Barnes J, et al. Results of the United Kingdom Children's Cancer Study Group first Wilms' Tumor Study. *J Clin Oncol* 1995;13:124–133.
- Clinical Laboratory Fee Schedule, Center for Medicare and Medicaid Services. <http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/clinlab.html>. Published 2012. Accessed March 2012.
- Vanderby SA, Babyn PS, Carter MW, et al. Effect of anesthesia and sedation on pediatric MR imaging patient flow. *Radiology* 2010;256:229–237.
- Teuffel O, Amir E, Alibhai SM, et al. Cost-effectiveness of outpatient management for febrile neutropenia in children with cancer. *Pediatrics* 2011;127:e279–e286.