Published in final edited form as:
J Pediatr Hematol Oncol. 2011 October ; 33(7): 521–523. doi:10.1097/MPH.0b013e31821b8dd5.

Barriers to the enrollment of children in the Children's Oncology Group study of very low risk Wilms tumor. A report from the Children's Oncology Group

Conrad V Fernandez, MD, FRCPC[1], **Ning Li, PhD**[2], **Elizabeth A Mullen, MD**[3], **Paul Grundy, MD**[4], **Elizabeth Perman, MD**[5], **Robert C Shamberger, MD**[6], **Peter Ehrlich, MD**[7], and **Jeffrey S. Dome, MD, PhD**[8]

[1]IWK Health Centre, Dalhousie University, Halifax, NS, Canada

[2]Children's Oncology Data Center, Epidemiology and Biostatistics College of Public Health & Professions, Gainesville, Florida, USA

[3]Dana Farber Cancer Institute, Harvard University, Boston MA, USA

[4]Stollery Children's Hospital, Edmonton, Alberta

[5]Children's Memorial Medical Center at Chicago, Chicago, Ill

[6]Children's Hospital Boston, Harvard University, Boston MA, USA

[7]C.S. Mott Children's Hospital, Ann Arbor, MI

[8]Children's National Medical Center, Washington, DC

Abstract

Very low risk (VLR) Wilms tumor is defined by favorable histology, age less than 2 years, tumor weight less than 550 grams and stage I. The Children's Oncology Group is currently studying a nephrectomy only strategy for these patients but the accrual rate is slightly below expected. 25 of 31 institutions responded with reasons by physicians and/or parents for electing not to participate. Parents were primarily concerned with the experimental nature of the study, whereas physicians were concerned about accurate staging, with some overlap. We point out the necessity of assessing these concerns in predicting feasibility of and accrual to a therapy reduction study.

Keywords

attitudes; very low risk; Wilms

Introduction

The current AREN0532 Children's Oncology Group (COG) Wilms tumor study is testing the hypothesis that children less than 2 years old with stage I favorable histology Wilms tumor weighing less than 550 grams can be effectively managed with nephrectomy only. A

Corresponding author and reprint requests: Conrad V Fernandez MD, IWK Health Centre, 5850 University Avenue, Halifax, Nova Scotia, B3K 6R8 Canada, Conrad.fernandez@iwk.nshealth.ca, Phone: 902-470-7290, Fax : 902-470-7216.

decisiontree analysis supports this as a reasonable strategy[1] and preliminary observations in eight patients demonstrated this to be plausible[2]. A larger study undertaken by Green et al[3], was halted because a stopping rule was reached when the relapse rate exceeded 10%. This stopping rule was set anticipating that the salvage rate would be only 50%. However, a much higher rate of more than 90% was observed[3] and in longer term follow up this has been maintained[4].

Advantages of nephrectomy alone as a treatment strategy in this very young patient population include avoiding chemotherapy in the majority (estimated to be more than 85%), thereby limiting the risk of veno-occlusive disease (up to 5%) [5], decreasing clinic or hospital visits, and avoiding central venous access devices. Standard treatment in this group of patients in North America would usually be considered as regimen EE4A (vincristine and actinomycin D × 18 weeks) although vincristine alone has also been used successfully[6]. A disadvantage of the nephrectomy only strategy is that patients with recurrence typically receive a more intensive regimen than they would have with Regimen DD4A (vincristine, actinomycin D, doxorubicin×24 weeks and involved field radiotherapy). In addition there is a theoretically greater psychological burden for parents during the observation period[7].

Review of National Wilms Tumor Study-5 (NWTS-5) data demonstrated that approximately 75% of eligible patients were enrolled on the observation only arm of the Green et al study (Breslow NWTS personal communication). Those who did not enroll were not formally surveyed, but sporadically recorded reasons for lack of enrollment included parental refusal, physician choice and ‘medically ineligible’. The current observation only arm of the AREN0532 study was projected to accrue 20–25 patients per year over 5 years based on the experience of NWTS5. We have noted a slightly lower accrual rate on the observation only arm compared to other renal tumor studies and exploration of this observation demonstrated that approximately 40% of eligible patients were not enrolled.

We therefore surveyed all institutions with potentially eligible patients who did not enroll on AREN0532 to determine reasons and outcomes for non-enrolled patients. We speculated that a large portion of non-enrollment was due to parental refusal, or that treating physicians consider nephrectomy only the current standard of care. Understanding the determinants of enrollment will be important to future study design, especially when a reduction in therapy question is at stake, and potentially important in addressing parental concerns.

Materials and Methods

COG Renal tumors study design

All patients with suspected renal tumors are eligible to be enrolled on a biology and classification study (AREN03B2). This study utilizes central review of radiology, pathology and surgical reports to assign an initial risk assignment. Patients found to meet the criteria for VLR (age < 2 years, stage I, favorable histology WT, weight < 550 grams) are then eligible to enroll on the observation only arm of AREN0532. To be eligible for this VLR arm, patients must have had lymph nodes sampled and be enrolled by 30 days following nephrectomy.

VLR Attitudes and practice study

Approval for this VLR attitudes and practice study was obtained from the IWK Health Centre Research Ethics Board, the chair of the renal tumors committee and the chair of the COG. Patients with VLR Wilms tumor enrolled on the classification and banking study (AREN03B2) were identified through the COG statistics office. This list was then used to identify VLR patients not enrolled on AREN0532 and the appropriate institutional lead Clinical Research Associate (CRA) contact person for that patient. An email cover letter was

sent to the institutional CRA containing an attached brief four item questionnaire with two reminders for non-respondents (questionnaire available from corresponding author). The questionnaire was developed by the authors (all experts in the care of children with renal tumors) to address both physician and parent concerns and listed seven options of the main possible reasons for not enrolling on study and a text field was provided for additional comment. The institutional CRA was asked to complete the questionnaire with the treating physician. No parental contact was requested. Patients were identified by registration number only and associated institutions were not recorded in the final data file.

Completed questionnaires were returned by email or fax and data entered and analyzed in an Excel file. Simple descriptive statistics were used to describe the results.

Results

78 patients were classified through registration on AREN03B2 between November 2006 (when AREN0532 opened to accrual) and May 2009 with stage I, favorable histology Wilms tumor with a tumor weight of < 550 grams and less than 2 years of age. Eight of these patients would have been classified as VLR but did not have adequate lymph node sampling. Thus 70 patients were classified as VLR. During this time period, 39 VLR patients enrolled and 31 eligible patients did not enroll on the AREN0532 observation study.

25 of 31 patients (81%) had completed questionnaires submitted by the institutional CRA. One questionnaire had a single missing response. Two CRAs specifically declined to take part and four did not respond. The CRAs were surveyed a median of 16 months from potential enrolment of the patient (range 2–32 months). The decision not to enroll was reported to be primarily physician-based in 10/25 and primarily parent-based in 14/25. One institution did not attribute a primary decision-maker. The physician decided not to open the study in two institutions and one additional institution indicated the study was not open but did not indicate if this was a physician decision or merely an issue of timing. The reasons for non-enrollment are described in Table 1 (more than one reason could be selected by respondents).

Patient outcomes

19 of the 25 patients received regimen EE4A (vincristine and dactinomycin) and five reported observation alone, with no chemotherapy. One respondent did not indicate treatment or an outcome. There were no relapses or deaths in any of the respondents at a relatively early median follow-up 17 months after diagnosis (range 3–33 months).

Discussion

As pediatric oncology therapies move to a more risk-based approach with the goal of maximizing survival while minimizing toxicity, certain patients may receive less therapy than traditional regimens. We found that lower than expected participation in such a study in Wilms tumor was driven by a mix of concerns from parents and physicians. Almost half of eligible VLR patients did not enroll on the observation only arm of AREN0532. Both groups cited having a primary concern that observation alone is insufficient therapy and/or that planned salvage therapy was too intense.

An additional concern raised by a substantial portion of the physicians was that patient biological parameters placed their patient too close to the exclusion criteria (for example borderline surgical margins) and therefore at increased risk of relapse. This is reflected in table 1 as “staging uncertainty”. The current AREN0532 study design modifies eligibility criteria from Green et al[3] to require lymph node sampling and exclude predisposition

syndromes to further reduce the risk of relapse. Additionally, central pathological review available on this study is meant to lessen institutional interpretation of biological risk[8]. Nonetheless, physician judgement of individual patient needs clearly plays a role in study enrollment. Ongoing discussion of the central review interpretation is encouraged with the primary study reviewers, if there is a discrepancy with institutional views.

The current AREN0532 study recommends fairly intensive computed tomography (CT) follow-up imaging with the rationale that early identification of relapse may benefit these VLR patients[9]. There has been increased discussion in the literature about the potential long term adverse risks of cumulative CT exposure[10, 11]. There has also been considerable debate at the study committee level regarding optimizing the risk/benefits in specifying follow up procedures and compliance with pediatric radiotherapy dosing[12]. However, the frequency and mode of diagnostic imaging were not cited as an issue by either by parents or physicians.

As this study was a retrospective report from the health care team perspective, we were not able to ascertain directly if parents had other concerns or if their concerns were accurately reflected. It is possible that the concerns attributed to parents, even if accurate, are more related to what was said to them by the physician about the study design than an intrinsic discomfort with the risk of observation only. Given the unavoidable influence of the health care team and the parents on each other, this would be difficult to disentangle, even if asked in a prospective manner. While we speculate that a psychological burden for parents waiting to see if their child might relapse may be a significant deterrent to enrollment[7, 13], we could not test this hypothesis in this study design. A strength of this study is the high return rate from institutions and thus we believe that we have a representative view of health care providers.

Prospective evaluation of parental and physician concerns might shed further light on decision-making. However, irrespective of the final attribution of the reasons for concern for enrolment, our study has identified concerns that should be heeded. One might infer that similar contributions are at play in other pediatric cancer trials with a study design of reduced intensity. Researchers should consider seeking endorsement of the research design by potentially enrolling physicians to more accurately determine feasibility and study accrual time lines. Although more challenging in parents, similar efforts might be made using surrogate parent representatives of children who have completed conventional therapy that is planned for subsequent study of intensity reduction[14].

Acknowledgments

This work is supported by NCCF U10 CA98543-02 and USPHS; CA-42326. We would like to acknowledge the work of the CRAs in submitting the completed questionnaires.

Research is supported by the Chair's Grant U10 CA98543 of the Children's Oncology Group from the National Cancer Institute, National Institutes of Health, Bethesda, MD, USA.

A complete listing of grant support for research conducted by CCG and POG before initiation of the COG grant in 2003 is available online at: http://www.childrensoncoogygroup.org/admin/grantinfo.htm

References

1. Frazier AL, Shamberger RC, Henderson TO, et al. Decision analysis to compare treatment strategies for Stage I/favorable histology Wilms tumor. Pediatr Blood Cancer. 2010; 54(7):879–884. [PubMed: 20052778]
2. Larsen E, Perez-Atayde A, Green DM, et al. Surgery only for the treatment of patients with stage I (Cassady) Wilms' tumor. Cancer. 1990; 66(2):264–266. [PubMed: 2164436]

3. Green DM, Breslow NE, Beckwith JB, et al. Treatment with nephrectomy only for small, stage I/favorable histology Wilms' tumor: a report from the National Wilms' Tumor Study Group. J Clin Oncol. 2001; 19(17):3719–3724. [PubMed: 11533093]
4. Shamberger RC, Anderson JR, Breslow NE, et al. Long-term outcomes for infants with very low risk Wilms tumor treated with surgery alone in National Wilms Tumor Study-5. Ann Surg. 2010; 251(3):555–558. [PubMed: 20142733]
5. Ludwig R, Weirich A, Abel U, et al. Hepatotoxicity in patients treated according to the nephroblastoma trial and study SIOP-9/GPOH. Med Pediatr Oncol. 1999; 33(5):462–469. [PubMed: 10531570]
6. Pritchard-Jones K, Kelsey A, Vujanic G, et al. Older age is an adverse prognostic factor in stage I, favorable histology Wilms' tumor treated with vincristine monochemotherapy: a study by the United Kingdom Children's Cancer Study Group, Wilm's Tumor Working Group. J Clin Oncol. 2003; 21(17):3269–3275. [PubMed: 12947062]
7. Norberg AL, Lindblad F, Boman KK. Parental traumatic stress during and after paediatric cancer treatment. Acta Oncol. 2005; 44(4):382–388. [PubMed: 16120547]
8. Dome JS, Cotton CA, Perlman EJ, et al. Treatment of anaplastic histology Wilms' tumor: results from the fifth National Wilms' Tumor Study. J Clin Oncol. 2006; 24(15):2352–2358. [PubMed: 16710034]
9. Owens CM, Veys PA, Pritchard J, et al. Role of chest computed tomography at diagnosis in the management of Wilms' tumor: a study by the United Kingdom Children's Cancer Study Group. J Clin Oncol. 2002; 20(12):2768–2773. [PubMed: 12065552]
10. Huda W. Radiation doses and risks in chest computed tomography examinations. Proc Am Thorac Soc. 2007; 4(4):316–320. [PubMed: 17652493]
11. Robbins E. Radiation risks from imaging studies in children with cancer. Pediatr Blood Cancer. 2008; 51(4):453–457. [PubMed: 18465805]
12. Singh S, Kalra MK, Moore MA, et al. Dose reduction and compliance with pediatric CT protocols adapted to patient size, clinical indication, and number of prior studies. Radiology. 2009; 252(1): 200–208. [PubMed: 19435938]
13. Lampic C, Wennberg A, Schill JE, et al. Anxiety and cancer-related worry of cancer patients at routine follow-up visits. Acta Oncol. 1994; 33(2):119–125. [PubMed: 8204268]
14. Boman K, Lindahl A, Bjork O. Disease-related distress in parents of children with cancer at various stages after the time of diagnosis. Acta Oncol. 2003; 42(2):137–146. [PubMed: 12801132]

Table 1

Reasons attributed to parents and physicians with respect to declining enrollment on a Children's Oncology Group observation only study for very low risk Wilms tumor.

Reason for not enrolling on observation only study	Parents N= 14	Physicians N = 10
EE4A chemotherapy better option	10	4
Observation too experimental	6	0
Concern about salvage intensity	5	2
Intensity of CT monitoring too high	0	0
AREN0532 study not open	0	2
Central line already placed	1	2
Staging uncertainty	0	6

Note: respondents could select more than one reason.