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Outcome of Patients with Relapsed or Progressive Ewing Sarcoma Enrolled on Cooperative Group Phase 2 Clinical Trials: a Report from the Children's Oncology Group

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Children's Oncology Group Data Sharing Statement
The Children's Oncology Group Data Sharing policy describes the release and use of COG individual subject data for use in research projects in accordance with National Clinical Trials Network (NCTN) Program and NCI Community Oncology Research Program (NCORP) Guidelines. Only data expressly released from the oversight of the relevant COG Data and Safety Monitoring Committee (DSMC) are available to be shared. Data sharing will ordinarily be considered only after the primary study manuscript is accepted for publication. For phase 3 studies, individual-level de-identified datasets that would be sufficient to reproduce results provided in a publication containing the primary study analysis can be requested from the NCTN/NCORP Data Archive at https://nctn-data-archive.nci.nih.gov/. Data are available to researchers who wish to analyze the data in secondary studies to enhance the public health benefit of the original work and agree to the terms and conditions of use. For non-phase 3 studies, data are available following the primary publication. An individual-level de-identified dataset containing the variables analyzed in the primary results paper can be expected to be available upon request. Requests for access to COG protocol research data should be sent to: datarequest@childrensoncologygroup.org. Data are available to researchers whose proposed analysis is found by COG to be feasible and of scientific merit and who agree to the terms and conditions of use.
For all requests, no other study documents, including the protocol, will be made available and no end date exists for requests. In addition to above, release of data collected in a clinical trial conducted under a binding collaborative agreement between COG or the NCI Cancer Therapy Evaluation Program (CTEP) and a pharmaceutical/biotechnology company must comply with the data sharing terms of the binding collaborative/contractual agreement and must receive the proper approvals.

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Abstract

Seven Children's Oncology Group phase 2 trials for patients with relapsed/progressive solid tumors were analyzed to estimate the event-free survival (EFS) for relapsed/progressive Ewing sarcoma. One hundred twenty-eight Ewing sarcoma patients were enrolled and 124 events occurred. The 6-month EFS was 12.7%, demonstrating the poor outcome of these patients. Only docetaxel achieved its protocol-specified radiographic response rate for activity; however, the EFS for docetaxel was similar to other agents, indicating that a higher radiographic response rate may not translate into superior disease control. This EFS benchmark could be utilized as an additional endpoint in trials for recurrent Ewing sarcoma.

Keywords

Ewing sarcoma; Outcome; Event-free Survival; Relapsed; Phase II trials; Objective response

Introduction

Ewing sarcoma is the second most common bone tumor of children and young adults.[1] While time and dose intense chemotherapy trials have improved the event-free survival (EFS) to over 70% for patients with localized disease, the prognosis for patients with metastatic or relapsed disease remains poor.[2–4]

The Children's Oncology Group (COG) and its legacy groups conducted seven single agent phase II trials for patients with relapsed or progressive solid tumors, each with a Ewing sarcoma cohort. Radiographic response rate was the primary outcome.[5–11] This pooled analysis of those trials was undertaken to establish a benchmark EFS for patients with relapsed/progressive Ewing sarcoma to inform study designs and outcome measures for future trials of novel agents.

Methods

Patients and protocols

Seven phase II trials for children with relapsed/progressive solid tumors with a Ewing sarcoma cohort conducted from 1997 until 2007 were included. No COG single agent phase II trial for solid tumors during this timeframe was excluded. Protocols were approved by local institutional review boards. Informed consent was obtained from all patients/guardians.

All patients enrolled were observed prospectively until disease progression, death, loss to follow-up, or a minimum of 5 years after enrollment (whichever occurred first). Table 1 lists the study drug, dose, primary endpoint, number of Ewing sarcoma enrollees, and drug activity conclusion from each trial. Studies used either a two-stage or three-stage design with null response rates of either 5% or 10% and alternative response rates of 25% or 30%.

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Statistical Methods

All patients enrolled were included in this analysis, including those unevaluable for the primary trial endpoint. The cutoff dates for data preparation for each of the trials are identified in the primary publication for each trial.

EFS, defined as time from trial enrollment until date of last contact, disease progression or death, was calculated for each patient. Patients who died or experienced disease progression were considered to have an EFS event; otherwise, the patient was considered censored at the date of last follow-up. EFS was a function of time since trial enrollment and was estimated according to the Kaplan-Meier method.[12] Patients who stopped protocol therapy because of patient or family preference or because of toxicity and who subsequently died without reporting the date of disease recurrence were considered to have disease progression at the time of death.

The equality of risk for EFS event across groups was assessed using the relative risk regression model with the potential prognostic factors of number of prior regimens, age at diagnosis, age at enrollment, sex, or race.[13] A two-sided P value ≤ 0.05 was considered evidence of a significant difference in risk for EFS event across the categories considered. Docetaxel was compared to the non-docetaxel trials using log rank test.

Five patients were enrolled on more than one trial. The variance of relative hazard estimates were calculated using the robust estimator accounting for the 5 clusters of two patients each.[14]

All analyses were done using STATA 16 (StatCorp, College Station Tx).

Results

One hundred twenty-eight patients with relapsed or progressive Ewing sarcoma were enrolled on the seven trials. The only trial that identified the study agent as demonstrating sufficient efficacy was CCG-0962 (docetaxel) with 3 partial responders (PR) out of 26 patients. While considered inactive, two PRs were observed on A09713 (topotecan), and one PR was observed on ADVL0122 (imatinib) [Table 1].[5–11]

One hundred twenty-four events occurred. One hundred six patients relapsed and 18 patients died as the first event. No deaths were due to drug toxicity. For all trials combined, the estimated 6-month EFS is 12.7% (95% confidence interval (CI) 7.6-19%) [Fig. 1].

The estimated 6-month EFS for CCG-0962 (docetaxel) was 15.4% (95% CI 4.8-31.5%). This result is not significantly different from the 12% (95% CI 6.6-19.2%) 6-month EFS estimate for the other 6 trials in aggregate (p=0.253; Supplemental Figure S1). Risk for an event was not significantly different across the seven trials considered in this analysis (Supplemental Table S1; Supplemental Figure S2). The evaluated potential prognostic factors of number of prior regimens, age at diagnosis, age at enrollment, sex, or race were not statistically significant (Supplemental Table S2).

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Discussion

This analysis demonstrates the poor survival of patients with relapsed or progressive Ewing sarcoma with measurable disease with an estimated 6-month EFS of 12.7%. Given the similarities across these agents, this 6-month EFS likely represents the natural history of the disease.

Radiographic response was the outcome measure for these trials. The ability of objective response rate (ORR) alone to predict improved survival and clinical benefit has been questioned.[15, 16] While Ewing sarcomas will often shrink with cytotoxic chemotherapy, the lack of shrinkage does not necessarily reflect the biological response.[15, 17] ORR does not account for potential clinical benefit of stable disease (SD). Studies have shown that the survival of patients with sarcomas with SD can be similar to the survival of patients with PR.[15, 16, 18] CCG 09713 (topotecan) demonstrated 2 PR and 3 SD. These results did not meet the protocol definition for activity despite having a 13.6% SD rate.[8] Subsequently the combination of topotecan and cyclophosphamide demonstrated activity and has been trialed in newly diagnosed patients.[19] The Japanese Orthopaedic Association demonstrated no difference in outcome for newly diagnosed patients with Ewing sarcoma with a best response of PR or SD.[18] Likewise, an analysis of radiographic response and survival for 241 patients on the rEECur trial demonstrated that participants with SD had similar PFS and overall survival compared to those with objective responses.[20]

We would recommend utilizing this 6-month EFS benchmark as an additional endpoint in phase 2 trials for patients with measurable disease in order to account for the clinical benefit of SD and to mitigate some of the potential issues of relying solely on ORR. For example, some non-cytotoxic agents may prolong time to progression without achieving an objective response. Such agents may nevertheless be of interest to study in the context of frontline therapy.

There are several limitations to this analysis. The most recent trial in this analysis concluded in October 2007. Since 2007, more combination or targeted therapy studies have been conducted. Also, the schedule of radiographic evaluation varies across studies, although generally at the completion of a 21- or 28-day cycle. Therefore, we focused on the 6-month EFS, which is the time point by which approximately 90% of the events had occurred, thus decreasing the effect on EFS estimate. We also do not have the data to analyze other factors known to influence outcome, specifically time to first recurrence and the extent of disease at diagnosis or relapse.[3] Not being able to control for these factors could bias the EFS estimate. Moreover, this patient population was heterogeneous and heavily pre-treated, with approximately half of the patients having already received two or more prior lines of therapy. This pre-treatment potentially changed the biology of the tumor thus potentially affecting the applicability of the results to newly diagnosed patients.

We have demonstrated the poor outcome of patients with relapsed/progressive Ewing sarcoma on seven COG and legacy group single agent phase 2 trials. The analysis provides a benchmark of an additional endpoint (EFS at 6 months) to be utilized in trials of novel

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agents, either as monotherapy or in combination, for patients with measurable relapsed/progressive Ewing sarcoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviation

COG	Children's Oncology Group
EFS	event-free survival
CI	confidence interval
ORR	Objective response rate
POG	Pediatric Oncology Group
CCG	Children's Cancer Group
WHO	World Health Organization
RECIST	response evaluation criteria in solid tumors
PR	partial response
PFS	progression free survival
SD	stable disease

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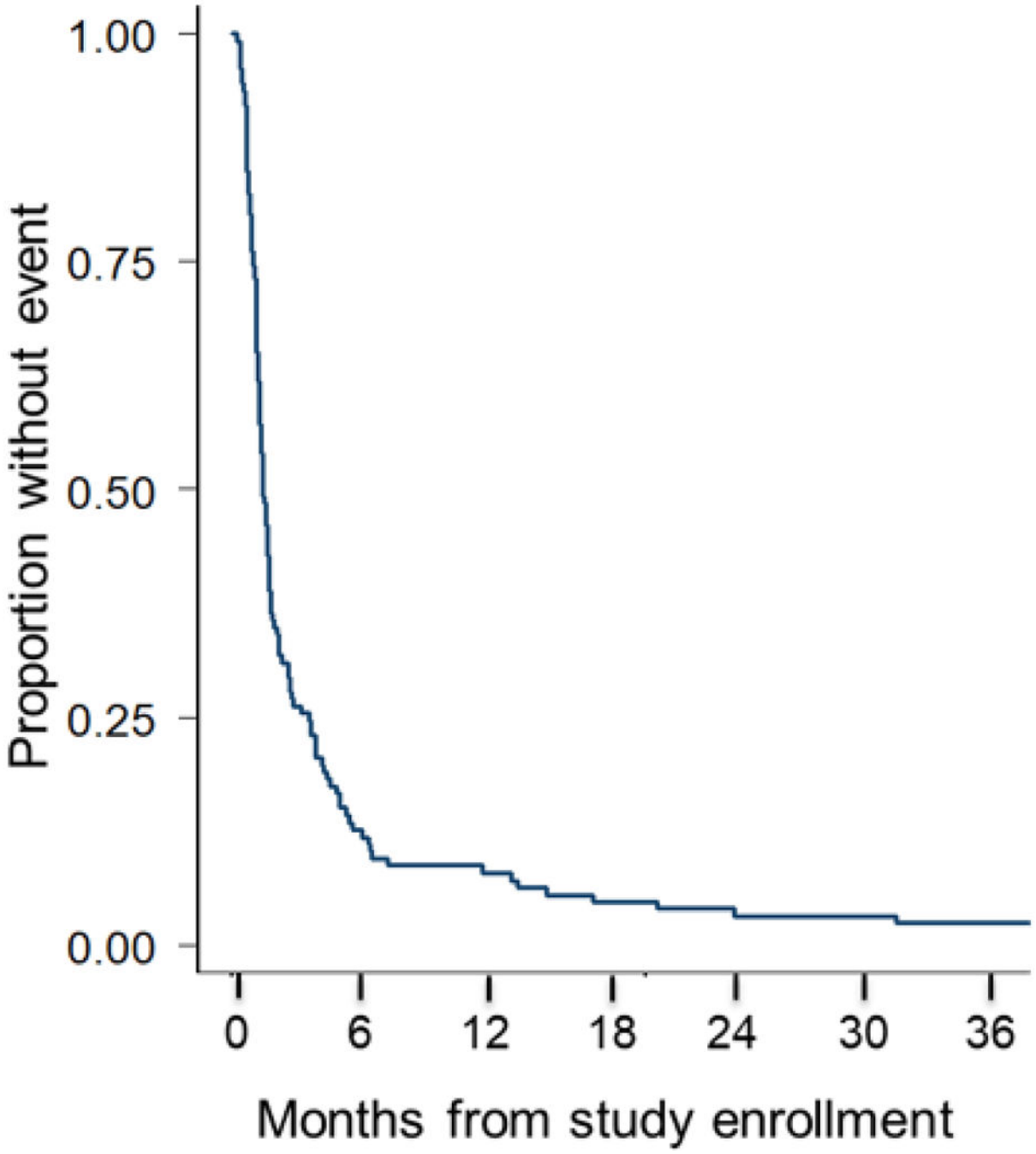

FIGURE 1.
Event free survival of the entire cohort of patients with relapsed or progressive Ewing sarcoma enrolled on the seven phase II trials. (n=128)

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TABLE 1

Characteristics and outcomes of the seven phase 2 monotherapy trials that included patients with Ewing sarcoma.

Study [ref.]	Years open	Agent (dose)	End Point (criteria)	No. of enrolled EWS patients	No. of EWS with best response	Activity for EWS according to study endpoint
CCG-0962[15]	1997-2001	Docetaxel (125 mg/m^2 every 21 days)	Radiographic (WHO)	26	3 PR	Effective
CCG 09713[12]	1999-2003	Topotecan (0.3 mg/m^2 continuous 21 day infusion every 28 days)	Radiographic (WHO)	22	2 PR/3 SD	No activity
POG 9761[10]	1999-2001	Irinotecan (50 mg/m^2/day for 5 days every 21 days)	Radiographic (RECIST)	18	0	No activity
POG 9963[14]	2000-2003	Rebeccamycin analogue (650 mg/m^2 every 21 days)	Radiographic (RECIST)	15	0	No activity
COG ADVL0122[11]	2002-2004	Imatinib (440 mg/m^2/day)	Radiographic (RECIST)	26	1 PR	No activity
COG ADVL0421[9]	2004-2005	Oxaliplatin (130 mg/m^2 every 21 days)	Radiographic (RECIST)	12	1 SD	No activity
COG ADVL0524[13]	2006-2007	Ixabepilone (8 mg/m^2/day for 5 days every 21 days)	Radiographic (RECIST)	9	0	No activity

EWS=Ewing sarcoma; PR= partial response; SD=stable disease; ref.=reference