HHS Public Access

Author manuscript

Pediatr Blood Cancer. Author manuscript; available in PMC 2015 September 26.

Published in final edited form as:

Pediatr Blood Cancer. 2013 March ; 60(3): 409–414. doi:10.1002/pbc.24328.

A Pilot Study of Low-Dose Anti-angiogenic Chemotherapy in Combination with Standard Multiagent Chemotherapy for Patients with Newly Diagnosed Metastatic Ewing Sarcoma Family of Tumors: A Children's Oncology Group (COG) Phase II Study

Judy L. Felgenhauer, MD[1], **Michael L. Nieder, MD**[2], **Mark D. Krailo, PhD**[3], **Mark L. Bernstein, MD**[4], **David W. Henry, MS**[5], **David Malkin, MD**[6], **Sylvain Baruchel, MD**[7], **Paul J. Chuba, MD, PhD**[8], **Scott L. Sailer, MD**[9], **Ken Brown, MD**[10], **Sarangarajan Ranganathan, MD**[11], and **Neyssa Marina, MD**[12]

[1]Providence Sacred Heart Medical Center and Children's Hospital, Spokane, WA.

[2]All Children's Hospital, St Petersburg, FL

[3]Keck School of Medicine, University of Southern California, Los Angeles, CA.

[4]IWK Health Center, Halifax, Nova Scotia, Canada.

[5]University of Kansas Medical Center, Kansas City, KS.

[6]The Hospital for Sick Children, Toronto, Ontario, Canada.

[7]The Hospital for Sick Children, Toronto, Ontario, Canada.

[8]Saint John Van Elslander Cancer Center, Grosse Pointe, MI.

[9]Wake Radiology Oncology Services, Cary, NC.

[10]British Columbia Children's Hospital, Vancouver, British Columbia, Canada.

[11]Children's Hospital of Pittsburgh, Pittsburgh, PA.

[12]Lucile Packard Children's Hospital Stanford University, Palo Alto, CA.

Abstract

Background—The aims of this study were to determine the feasibility of the combination of low dose, anti-angiogenic chemotherapy with standard therapy for patients with metastatic Ewing sarcoma (ES), and to obtain preliminary outcome data.

Procedures—Patients with metastatic ES were eligible. Therapy consisted of alternating cycles of ifosfamide-etoposide, and vincristine, doxorubicin, cyclophosphamide. Vinblastine and

Corresponding Author: Judy Felgenhauer, MD, Providence Sacred Heart Medical Center and Children's Hospital, 101 W 8th Avenue, Spokane, Washington 99202, Telephone: 509.474.3023, Facsimile: 509.474.6222, judy.felgenhauer@providence.org.

Conflict of Interest Statement: There are no conflicts of interests identified by the authors.

celecoxib were concomitantly administered. Surgical, radiotherapeutic or combination local control therapy was given per institutional preference.

Results—Thirty-five eligible patients were enrolled. Ninety percent received at least 75% of planned vinblastine/celecoxib doses. There was no excess of neurologic, infectious, hemorrhagic or cardiovascular toxicities. However, seven of 21 patients who received pulmonary irradiation prior to experiencing pulmonary toxicity did develop grade 2 or greater pulmonary toxicity, including two deaths of apparent radiation pneumonitis. Fourteen of 16 patients with pelvic disease received local irradiation. Hemorrhagic cystitis developed in six patients, five of whom had received pelvic irradiation. The overall twenty-four month event free survival was 35% (19–51%); 71% (26–92%) for the seven with isolated pulmonary metastases, 26% (10–45%) for all others.

Conclusion—The combination of vinblastine/celecoxib metronomic therapy with standard ES treatment was feasible according to the protocol definitions. However, excess toxicity in irradiated areas was noted and limits the usefulness of this protocol. The 24-month EFS for those with isolated pulmonary metastases is better than historical controls, although the number of patient number is small, follow up short and we are lacking contemporaneous controls.

Keywords

Ewing sarcoma; antiangiogenic agents; cystitis; radiation pneumonitis

INTRODUCTION

Patients with metastatic Ewing sarcoma family of tumors (ES) continue to have a poor outcome with a three year survival of 20% despite the use of dose-intensified chemotherapy.[1,2,3] Intensification of therapy by escalation of doses of the standard five-drugs (vincristine, doxorubicin, cyclophosphamide, ifosfamide, etoposide) has not been successful in improving outcomes. Alternate dosing schedules such as dose intensification by interval compression of the most active agents have recently been shown to increase the survival of localized ES patients.[4] Historically, however, strategies that improved the outcome for patients with localized disease have not yielded similar results for patients with metastatic disease.[5] Although high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation may increase short term survival, there is no evidence that five-year survival is improved with this approach.[6,7]

In the early 2000s Browder et al and Klement et al described a regimen of frequent dosing of cyclophosphamide or vinblastine that was termed anti-angiogenic scheduling as angiogenesis inhibition was shown to be responsible for the observed anti-tumor effect.[8,9], Anti-angiogenic scheduling probably does not solely rely on anti-angiogenic effects, making the term anti-angiogenic therapy too simplistic.[10] The different mechanisms of action are postulated to be from normalization of tumor vasculature to prevention of rapid tumor cell re-population following chemotherapy to potentiation of the anti-vascular activity of chemotherapy.[11,12]

The present trial was designed to determine the feasibility and safety of administering a low-dose regimen of anti-angiogenic scheduled chemotherapy with vinblastine and celecoxib, in combination with standard multiagent chemotherapy for patients with metastatic ES. Vinblastine and celecoxib were selected as the anti-angiogenic agents because of their availability, presumed low toxicity and preliminary data suggesting anti-angiogenic effects.[13] In addition, the pharmacokinetics (PK) of celecoxib in combination with vinblastine in the setting of concomitant intensive cytotoxic chemotherapy were to be evaluated in patients choosing to participate in the PK studies.

METHODS

Eligibility Criteria

Patients < 50 years of age with newly diagnosed ES of bone or soft tissue metastatic to bone and/or bone marrow with a body surface area of at least 0.4 m^2 (to allow for the minimal dosing of celecoxib) were eligible for COG study AEWS02P1. Patients with metastases isolated to the lung were eligible, although the priority was enrollment on COG study AEWS0331, which had similar eligibility criteria. Other eligibility requirements included adequate renal, hepatic and cardiac function at diagnosis and a Karnofsky or Lansky performance score greater or equal to 50%, as appropriate for age. All patients or guardians gave written informed consent. Patients with sulfa allergy, aspirin hypersensitivity, or asthma triad (asthma with nasal polyps, and urticaria) were not eligible for the protocol in order to avoid possible reactions to celecoxib, nor were patients with primary lesions of the central nervous system.

Therapy

Treatment occurred in three phases: Induction (the first four cycles of chemotherapy), Local Control (usually beginning at Week 13), and Consolidation (10 additional cycles of chemotherapy) for a total of 14 cycles of chemotherapy. Induction and consolidation consisted of alternating chemotherapy cycles A and B given at three-week intervals. Cycle A was vincristine (1.5 mg/m^2 day 1), doxorubicin (37.5 mg/m^2/day on day 1 & 2), and cyclophosphamide (1200 mg/m^2 on day 1). Cycle B consisted of ifosfamide (1800 mg/m^2/day on days 1–5) and etoposide (100 mg/m^2/day on days 1–5). MESNA was used as an uroprotectant with cyclophosphamide and ifosfamide. G-CSF (filgrastim or PEG filgrastim) was used after each cycle. The first six patients enrolled received vinblastine but not celecoxib during the first two induction chemotherapy cycles (VAdriaC, IE; weeks 1–6).

Vinblastine was given as 1 mg/m^2/dose IV push three times per week beginning Day 1 of Cycle 1 and continuing through Day 21 of Cycle 14. Vinblastine was only given twice per week during weeks when patients were scheduled to receive vincristine. Celecoxib (250 mg/m^2/bid, the dose rounded off to the nearest 100 mg, no maximum dose) was given from Day 1 of Cycle 1 through Day 21 of Cycle 14. An amendment several months after the protocol was opened allowed for the vinblastine and celecoxib to be withheld for up to seven days perioperatively during the local control phase.

Patients were reassessed after 12 weeks of therapy. Local control plans for the primary site were determined by the local institution. Local control could take four different forms; surgery only, radiation alone, preoperative radiation followed by surgery, or surgery followed by radiation therapy. Surgical resection of the primary site was encouraged as part of local control at week 13 if it was believed that the lesion could be resected with negative margins and a reasonable functional outcome. If the patient was to have preoperative radiation, surgery was scheduled after recovery from radiotherapy and after cycle 7 of chemotherapy. Patients who had unresectable lesions or inadequate margins after surgery received radiation therapy to their primary site. The protocol directed that all patients with lung metastases were to receive 1500 cGy of whole lung irradiation, generally at week 13 of therapy. Metastatic sites were to be irradiated with the caveat that for patients with widespread metastatic disease, care was to be taken not to treat more than 50% of active bone marrow.

Materials and Methods

Blood was to be collected on days 1 and 8 at multiple time intervals to determine the pharmacokinetics of celecoxib. Samples for vinblastine kinetics were collected at the beginning of week two (see Supplemental Appendix I). This was optional for patients.

Statistical Methods

The study was designed to assess the feasibility and safety of adding anti-angiogenic agents to standard chemotherapy. The regimen was to be considered feasible to administer if anti-angiogenic therapy could be delivered for at least 75% of days required by the protocol to 25 or more eligible patients. Tolerability was assessed primarily by monitoring patients for the occurrence of grade 3 or higher neurological adverse experiences, grade 4 infection, mucositis or gastrointestinal bleeding at any time during protocol therapy. Interim safety monitoring was done after the first six and again after the first 12 patients were enrolled. If two or more of 12 patients experienced any one of the monitored toxicities (except for a neuropathy that resolved within one week), the study was to be flagged for modification. If the therapy was considered tolerable after the initial evaluation, a total of 36 patients were to be enrolled. If seven or more of 36 patients experienced any one of the monitored toxicities, the therapy was to be considered too toxic. The overall toxic death rate for the study was monitored. The therapy was to be considered to have an excessive toxic death rate if three treatment-related deaths occurred in the first 18 patients or four such deaths occurred among the 36 patients.

Event-free survival (EFS) was defined as the time from study entry until disease progression, detection of a second malignant neoplasm (SMN), death or last patient contact, whichever came first. Patients who had disease progression, SMN or died were considered to have experienced an event; otherwise the patient was considered censored at the time of last follow up. The EFS was evaluated by the Kaplan-Meier method.[14] The cumulative incidence of second malignant neoplasms was estimated using the method of Gray.[15]

The prognostic effect of sex (male *v.* female), race (Caucasian *v.* non-Caucasian) and ethnicity (Hispanic *v.* non-Hispanic) based on the particular patient characteristic as reported

by the patient or parent was assessed. The study population was divided according to the grouping listed above and the equality of risk for EFS-event was tested by the log-rank test.[14] A p-value of 0.05 or less was considered indicative of a significant difference in risk between the particular subgroups.

Pharmacokinetic and Statistical Analysis for PK studies—Estimates of PK parameters for celecoxib and vinblastine were derived by noncompartmental analysis using the software package WinNonlin (v.5.2, Pharsight Corporation, St. Louis, Missouri). The pharmacokinetic parameters derived for each patient for celecoxib and vinblastine are presented in the Supplemental Appendix II.

RESULTS

The study opened for enrollment in March 2004 and closed to patient entry in April of 2008. Data current to April 30, 2009 were used for this analysis. Thirty-eight (38) patients were enrolled. However, three were later found to be ineligible (one patient was declared ineligible during an audit after the protocol had been closed): two patients did not have metastatic disease and the third had lymphoblastic lymphoma. These three patients were not included in the analysis.

The first six patients who received only vinblastine during the first two induction chemotherapy cycles demonstrated no unusual toxicities; these six patients then had celecoxib added to their vinblastine during the next two induction cycles (VAdriaC, IE; weeks 7–12). The study then closed to accrual until these six patients completed induction and were evaluated for excessive or unusual toxicities. During the closure, concerns regarding the cardiotoxicity of nonsteroidal anti-inflammatory agents in adult trials were reported. When the protocol reopened, it included an amendment updating the informed consent document regarding possible cardiovascular complications with celecoxib.

Demographic characteristics are included in Table I and Supplemental Appendix III. Local therapy was planned for week 13. Three patients did not have local therapy; two had disease progression and one patient electively discontinued protocol therapy prior to week 13.

The monitoring criteria for serious adverse experiences and for toxic death were not exceeded. Thus, according to the criteria in the protocol, the therapy is considered tolerable although some worrisome toxicities were observed. The planned therapy was completed by 20 of the 35 eligible patients. One of the 20 patients died of radiation pneumonitis within 30 days of completing therapy. Progressive disease occurred in six patients while on therapy. Therapy was stopped early after refusal of further protocol therapy by four patients/families and one patient who moved to an institute where the protocol was not open. Toxicity in four patients led to cessation of the planned therapy: one from persistent hemorrhagic cystitis, one from GI bleeding, one for poor wound healing and one other death from radiation pneumonitis. The patient who was removed from protocol therapy for GI hemorrhage experienced two episodes, the first in the setting of inadequate protocol specified proton pump inhibition.

Ninety percent of patients reported receiving 75% or greater of their planned celecoxib/vinblastine doses while 7% had delays of greater than 10 days. Protocol specified dose limiting targeted toxicities are listed in Table II.

Grades 3 and 4 cardiac toxicities were required to be reported. One patient experienced a prolonged QTc that resolved within one week. Another patient who developed pulmonary hypertension was reported to have had a syncopal episode, pericardial effusion and cardiac ischemia prior to death from presumed radiation pneumonitis.

Eight patients were reported to have had grade 2 or greater pulmonary toxicity. Of these, seven developed pulmonary toxicity post radiation, including two deaths that appear to be related to radiation pneumonitis. Twenty-one (21) patients received pulmonary irradiation as a component of therapy for primary lesions or pulmonary metastatic disease. Only one of the 13 who did not receive prior pulmonary irradiation developed pulmonary toxicity (See Table III). In addition, another patient treated on the study, but later declared to be ineligible, had grade 4 pulmonary toxicity thought to be due to radiation pneumonitis.

Eight incidents of grade 2 or greater hemorrhagic cystitis were reported in six patients. Pelvic primary tumors were present in many of patients on this study (16/35). Of these 16, only three did not receive radiation to the pelvis. Of the six patients who developed hemorrhagic cystitis, five had their bladder included in a radiation field.

There have been two reports of secondary myelodysplastic syndrome following end of therapy. The 4 year cumulative incidence for secondary malignant neoplasm (SMN) is 9.0% (upper 95% confidence limit: 20%).

The estimated event free survival (EFS) at 24 months is 35% (95% confidence interval 19%–51%). Patients with isolated lung metastasis fared better with an EFS of 71% (CI 26–92%) as compared with all other patients whose EFS was only 26% (CI 10 to 45%; p = 0.034). No statistical difference in EFS in this limited patient population was seen based upon race, ethnicity or gender.

Pharmacokinetic data

At week one, celecoxib resulted in a median peak concentration (Cmax) three hours after drug administration, consistent with data previously published by Stempak et al. However the C_{max} is much higher and $t_{½}$ is longer compared with previous results (Table IV).[13,16] See additional data in Supplemental Appendix II

Peak concentration of vinblastine occurred at a median of two minutes after drug administration. The drug displayed a triphasic serum decay pattern with a rapid initial half-life of 12 minutes, followed by an intermediate middle half-life of 1.7 hours and a long terminal elimination half-life of 14.5 hours (Table V). These results are consistent with previous publications.[13,16]

DISCUSSION

The administration of celecoxib and vinblastine combined with standard multiagent chemotherapy was feasible as determined by the ability to administer 75% of the scheduled anti-angiogenic therapy to 90% of patients, more than the protocol targeted value of at least 70% of patients. We did not observe any excessive targeted toxicities, including neurologic complications, infections, mucositis and G.I. bleeding, or excessive delays in delivering the planned chemotherapy. Most of the toxicities we report are those commonly described with standard ES therapy. However, the unexpectedly frequent and severe pulmonary and bladder toxicities make this an approach that would require cautious application in future studies. Previous oncologic studies utilizing this combination of drugs have not described the radiation-related toxicities seen in this study.[1,2,4]

The Adenoma Prevention with Celecoxib (APC) study and other studies in adults have suggested that celecoxib causes increased risk of cardiac toxicity especially at higher doses.[17,18] Some studies have suggested that celecoxib may be less likely to cause adverse cardiovascular outcomes than rofecoxib, which was removed from the U.S. market.[19,20] Despite the concerns raised about celecoxib and cardiac toxicity after this protocol opened, excessive cardiac toxicity was not observed. The cardiac toxicity reported was primarily related to sepsis and respiratory failure. The dosage of celecoxib for this study was 250 mg/m^2 twice daily (approximately 16.6 mg/kg/day) and a maximum dose was not set, so larger patients received significantly higher doses than were used in the APC study. Additionally, patients in this study received doxorubicin. Studies using 6 to 12 mg/kg of celecoxib daily in juvenile rheumatoid arthritis did not report cardiac toxicity, (FDA approval announcement), nor did studies using 2–16 mg/kg/day for prevention of adenomatous polyps.[21,22,23] These studies were mostly in small numbers of children and for less than 6 months duration. Pharmacokinetic studies of celecoxib using the same doses as this study have shown no sign of cardiac toxicity for an average of 10 weeks of therapy, up to 18 months in one patient.[24] Pediatric patients may be at a lower risk for cardiac toxicity, at least when celecoxib is used for short periods of time.

The pulmonary toxicity seen in this study was concerning. There are few baseline data available in terms of the expected incidence of radiation pneumonitis in patients with Ewing sarcoma receiving pulmonary irradiation, but death resulting from that process is considered to be an uncommon event.[25,26,27], Lung toxicity has been described in adults receiving celecoxib with or without radiation.[28,29, 30] Adult doses of celecoxib were generally lower than our patients received as there was no maximum dose of celecoxib on this protocol. Celecoxib administration during radiation therapy appears to act as a radiosensitizer. Although more patient information is needed, our results suggest that celecoxib should be discontinued during radiation treatments.

Similarly the rate of hemorrhagic cystitis raises concerns. Cyclophosphamide, ifosfamide and radiation to the bladder are all known risk factors for hemorrhagic cystitis.[31] We were unable to find baseline incidence data from Ewing studies performed since the addition of MESNA as a uroprotectant. Hemorrhagic cystitis was described in 15% of ES patients receiving cyclophosphamide in the pre MESNA era, some of whom also received radiation

to the pelvis.[32] We do not have information about BK virus or adenoviral status in these patients, which if present, could certainly have contributed to the hemorrhagic cystitis.

It is unclear whether the reported GI toxicity could have been prevented by appropriate doses of a proton pump inhibitor. We also did not see any enhancement of hematologic toxicity. The incidence rate for SMN is consistent with that observed in prior studies, there is no evidence to suggest that anti-angiogenic agents potentiated this risk.[33]

We have shown that the addition of the anti-angiogenic agents vinblastine and celecoxib to standard ES therapy is feasible as described by the predefined protocol aims. However, as written, protocol administered therapy was complicated by high rates of pulmonary and bladder toxicity, possibly due to the use of local radiation therapy while vinblastine/celecoxib treatment was ongoing. Although our sample size was small, our findings suggest that the celecoxib/vinblastine may act as radiosensitizers, and should be withheld during radiation treatment. Whether other anti-angiogenic scheduled agents exhibit the same toxicity will require careful observation as new anti-angiogenic agents are employed.

Whereas an overall survival advantage was not observed when compared to historical controls, the two year event-free survival of patients with pulmonary metastases only was better than expected at 71%.[4,5] Previous studies have shown two year survival rates of 31% and 36% for this group.[4,5] The prudent use of an anti-angiogenic scheduled agents in combination with standard ES therapy may offer an alternative method with which to treat this otherwise poorly responsive disease but requires more investigation given the small number of patients and short follow up.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Pharmacokinetic analysis: Dr. Facundo Garcia Bournissen & Bing Wu

Mass spectrometry assay: Michael Leadley & Bing Wu, Hospital for Sick Children, supported by the Canadian Foundation for Innovation. Statistical support: Doojduen Villaluna, MS, Children’s Oncology Group, Arcadia, CA.

Research Support: COG Grant number CA98543

References

1. Grier HE, Krailo MD, Tarbell NJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. N Engl J Med. 2003; 348(8):694–701. [PubMed: 12594313]
2. Granowetter L, Womer R, Davidas M, et al. Dose-intensified compared with standard chemotherapy for nonmetastatic Ewing sarcoma family of tumors: a Children's Oncology Group Study. J Clin Oncol. 2009; 27(15):2536–2541. [PubMed: 19349548]
3. Cotterill SJ, Ahrens S, Paulussen M, et al. Prognostic factors in Ewing's tumor of bone: analysis of 975 patients from the European Intergroup Cooperative Ewing's Sarcoma Study Group. J Clin Oncol. 2000; 18:3108–3114. [PubMed: 10963639]

4. Womer RB, West DC, Krailo MD, et al. Randomized comparison of every-two-week v. every-three-week chemotherapy in Ewing family tumors (ESFT). Journal of Clinical Oncology. 2008; 26 (May 20 suppl; abstr 10504).
5. Miser JS, Goldsby RE, Chen Z, et al. Treatment of metastatic Ewing sarcoma/primitive neuroectodermal tumor of bone: evaluation of increasing the dose intensity of chemotherapy-a report from the Children's Oncology Group. Pediatr Blood Cancer. 2007; 49:894–900. [PubMed: 17584910]
6. Meyers PA, Krailo MD, Ladanyi M, et al. High-dose melphalan, etoposide, total-body irradiation, and autologous stem-cell reconstitution as consolidation therapy for high-risk Ewing's sarcoma does not improve prognosis. J Clin Oncol. 2001; 19:2812–2820. [PubMed: 11387352]
7. Ladenstein R, Pötschger U, Le Deley MC, et al. Primary disseminated multifocal Ewing sarcoma: results of the Euro-EWING 99 trial. J Clin Oncol. 2010; 10(28):3284–3291. [PubMed: 20547982]
8. Browder T, Butterfield CE, Kräling BM, et al. Anti-angiogenic scheduling of chemotherapy improves efficacy against experimental drug-resistant cancer. Cancer Res. 2000 Apr 1; 60(7):1878–1886. [PubMed: 10766175]
9. Klement G, Baruchel S, Rak J, et al. Continuous low-dose therapy with vinblastine and VEGF receptor-2 antibody induces sustained tumor regression without overt toxicity. J Clin Invest. 2000 Apr; 105(8):R15–R24. Erratum in: J Clin Invest. Oct. 2006:116(10):2827,.J Clin Invest. Nov 2006:116(11):3084. [PubMed: 10772661]
10. Pasquier E, Kavallaris M, André N. Metronomic chemotherapy: new rationale for new directions. Nat Rev Clin Oncol. 2010; 7(8):455–465. [PubMed: 20531380]
11. Kerbel RS. Anti-angiogenic therapy: a universal chemosensitization strategy for cancer? Science. 2006 May 26; 312(5777):1171–1175. [PubMed: 16728631]
12. Shaked Y, Kerbel RS. Antiangiogenic strategies on defense: on the possibility of blocking rebounds by the tumor vasculature after chemotherapy. Cancer Res. 2007; 67(15):7055–7058. [PubMed: 17671170]
13. Stempak D, Gammon J, Hatlon J, et al. A pilot pharmacokinetic and antiangiogenic biomarker study of celecoxib and low-dose metronomic vinblastine or cyclophosphamide in pediatric recurrent solid tumors. J Pediatr Hematol Oncol. 2006; 28:720–728. [PubMed: 17114958]
14. Kalbfleisch, JD.; Prentice, RL. The statistical analysis of failure time data. Second edition. New York: John Wiley and Sons; 2002.
15. Gray RJ. A class of k-sample multiple tests for comparing cumulative incidence of a competing risk. Ann Stat. 1988; 16:1141–1154.
16. Stempak D, Gammon J, Klein J. Single-dose and steady-state pharmacokinetics of celecoxib in children. Clin Pharmacol Ther. 2002; 72:490–497. [PubMed: 12426512]
17. Solomon SD, McMurray JJV, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med. 2005; 352:1071–1080. [PubMed: 15713944]
18. Graham DJ. Cox-2 inhibitors, other NSAIDs, and cardiovascular risk: the seduction of common sense. JAMA. 2006; 296:1653–1656. [PubMed: 16968830]
19. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. JAMA. 2006; 96:1633–1644. [PubMed: 16968831]
20. Kimmel SE, Berlin JA, Reilly M, et al. Patients exposed to rofecoxib and celecoxib have differential odds of nonfatal myocardial infarction. Ann Intern Med. 2005; 142:15764.
21. Foeldvari L, Szer IS, Zemel LS, et al. A prospective study comparing celecoxib with naproxen in children with juvenile rheumatoid arthritis. J Rheumatol. 2009; 36:174–182. [PubMed: 19012356]
22. Attard TM, Young RJ, Tajuori T, et al. P0787 safety and efficacy of celecoxib in children with familial adenomatous polyposis. J Pediatr Gastroenter Nutr. 2004; 39:S356.
23. Lynch PM, Ayers GD, Hawk E, et al. The safety and efficacy of celecoxib in children with familial adenomatous polyposis. Am J Gastroenterol. 2010; 105:1437–1443. [PubMed: 20234350]
24. Stempak D, Gammon J, Halton J, et al. Modulation of celecoxib pharmacokinetics by food in pediatric patients. Clin Pharmacol Ther. 2005; 77:226–228. [PubMed: 15735617]

25. Spunt SL, McCarvilee B, Kun LE, et al. Selective use of whole-lung irradiation for patients with Ewing sarcoma family tumors and pulmonary metastases at the time of diagnosis. J Ped. Hem. Onc. 2001; 23:93–98.

26. Abratt RP, Onc FR, Morgan GW, et al. Pulmonary complications of radiation therapy. Clin Chest Med. 2004; 25:167–177. [PubMed: 15062608]

27. Bölling T, Schuck A, Paulussen M, et al. Whole lung irradiation in patients with exclusively pulmonary metastases of Ewing tumors. Toxicity analysis and treatment results of the EICESS-92 trial. Strahlenther Onkol. 2008; 184(4):193–197. [PubMed: 18398583]

28. Liao Z, Komaki R, Milas L, et al. A phase I clinical trial of thoracic radiotherapy and concurrent celecoxib for patients with unfavorable performance statusinoperable/unresectable non-small cell lung cancer. Clin Cancer Res. 2005:113342–113348.

29. Argiris A, Kut V, Luong L, et al. Phase I and pharmacokinetic study of docetaxel, irinotecan, and celecoxib in patients with advanced non-small cell lung cancer. Invest New Drugs. 2006; 4(3): 203–212. [PubMed: 16096702]

30. Mutter R, Lu B, Carbone DP, et al. A phase II study of celecoxib in combination with paclitaxel, carboplain, and radiotherapy for patients with inoperable stage IIA/B non-small cell lung cancer. Clin Cancer Res. 2009; 15(6):2158–2165. [PubMed: 19276291]

31. Crew JP, Jephcott CR, Reynard JM. Radiation-induced haemorrhagic cystits. Euro Urol. 2001; 40:111–123.

32. Stillwell TJ, Benson RB, Burgert EO. Cyclophosphamide-induced hemorrhagic cystitis in Ewing's sarcoma. J Clin Oncol. 1988; 6:76–82. [PubMed: 3335893]

33. Bhatia S, Krailo MD, Chen Z, et al. Therapy-related myelodysplasia and acute myeloid leukemia after Ewing sarcoma and primitive neuroectodermal tumor of bone: a report from the Children's Oncology Group. Blood. 2007; 109:46–51. [PubMed: 16985182]

Table I

Clinical Characteristics n= 35

Characteristic	**No. of patients**
Sex M:F	21:14
Race	
White	28
African American	0
Primary tumor site	
Pelvis	16
Chest Wall	8
Other	11
Age range in years	
≤9	9
10–17	20
≥ 18	6
Sites of metastases	
Lung Only	7
Bone and/or bone marrow	24
Not lung only, no bone or bone marrow involvement	3
Not reported	1

Table II

Targeted Dose Limiting Toxicities

	Induction	Consolidation
Infection grade 4	1	3
Sensory neuropathy grade 3/4	2	1
GI bleeding		1

Table III

Pulmonary Toxicity

Patient Identifier	Toxicity	Grade[1]	Previous XRT to lungs	Presumed Etiology
2	Hypoxia	4	Yes	TRALI (transfusion related acute lung injury)
6	Hypoxia	3	No	Unknown
11	Hypoxia	4	Yes	Fluid overload with chemotherapy IVFs
12	ARDS	5	Yes	Radiation pneumonitis
19	Pneumonitis Cardiac failure	4 5	Yes	Radiation pneumonitis, Pulmonary HTN led to cardiac failure
21	Hemorrhagic bilateral pleural effusions	4	Yes	unknown
23	Hypoxia	4	Yes	Pneumonia
32	Hypoxia	3	Yes	Pneumonia

[1] Toxicities reported according to CTC AE criteria version 3.

Table IV

Celecoxib pharmacokinetic parameters in patients with metastatic Ewing sarcoma during week 1 and week 2

#	n	Dose (mg)	T_{max} (hr)	C_{max} (mcg/L)	C_{min} (mcg/L)	$AUC_{0–12}$ (mcg-hr/L)	V_d/F (L/kg)	Cl/F (L/h/kg)	$t_{½}$ (h)
Week 1	**7**	300 (median)	3 (median)	4548.27 ± 2552.91	299.958 ± 374.167	25754 ±11614	2 ± 1.3	0.21 ± 0.1	7.8 ± 0.4
Week 2	**6**	400 (median)	1 (median)	6267.132 ± 1725.06	632.88 ±522.698	33960 ± 9087	3.1 ± 2.2	0.29 ± 0.1	7.1 ± 4.0

Data are expressed as mean ± standard deviation Tmax = time of maximum plasma concentration; Cmax = maximum plasma concentration; Cmin = minimum plasma concentration; AUC = area under [the plasma] concentration [time curve]; Vd/F = apparent volume of distribution; Cl/F = apparent clearance; t½ = half life

Pediatr Blood Cancer. Author manuscript; available in PMC 2015 September 26.

Table 5

Vinblastine pharmacokinetic parameters in patients with metastatic Ewing sarcoma

All patients were treated with Vinblastine 1mg/m^2/d IV

Plasma samples were collected at pre- and 2 min, 0.5, 1, 3, 6, 12, and 24 hours post-dosing

Patient #	Dose (mg)	T_{max} (h)	C_{max} (mcg/L)	C_{min} (mcg/L)	$AUC_{0-\infty}$ (mcg-hr/L)	V_d/F (L/kg)	Cl/F (L/h/kg)	initial-$t_{½}$ (h)	middle-$t_{½}$ (h)	terminal-$t_{½}$ (h)
8	0.8	0.03	12.3	0	12.9112	37.2253	2.9506	0.1538	2.1168	8.745
13	1.8	1	12.6	*	34.23	2.3223	0.8078	0.243	1.0016	
17	1.8	0.03	60.3	*	31.0832	1.9416	0.8344	0.1632	1.5833	
18	1.7	0.03	37.9	0.22	24.9672	16.9011	1.1329	0.178	1.785	14.257
20	1.3	0.03	13.1	0.118	17.6481	28.2878	1.8696	0.2949	2.1434	13.2832
28	1.4	0.03	8.94	0.173	16.9606	58.9424	1.876	0.4494	1.5869	21.7781
Mean ± S.D.	1.47 ± 0.39	0.03 (median)	24.19 ± 20.6	0.13 ± 0.10	23 ± 8.5	24.3 ± 22.0	1.6 ± 0.8	0.2 ± 0.1	1.7 ± 0.4	14.5 ± 5.4

Data are expressed as mean ± standard deviation. Tmax= time of maximum plasma concentration: Cmax = maximum plasma concentration; Cmin = minimum plasma concentration, AUC = area under [the plasma] concentration [time curve]; Vd/F = apparent volume of distribution; Cl/F = apparent clearance; t½ = half life

* = data insufficient for calculation