Title

Neoadjuvant pazopanib in nonrhabdomyosarcoma soft tissue sarcomas (ARST1321): A report of major wound complications from the Childrens Oncology Group and NRG Oncology.

Journal

Seminars in Surgical Oncology, 127(5)

Authors

Sorger, Joel

Hawkins, Douglas

Spunt, Sheri

et al.

Publication Date

2023-04-01

DOI

10.1002/jso.27205

Peer reviewed

HHS Public Access

Author manuscript

J Surg Oncol. Author manuscript; available in PMC 2024 April 01.

Published in final edited form as:

J Surg Oncol. 2023 April ; 127(5): 871–881. doi:10.1002/jso.27205.

NEOADJUVANT PAZOPANIB IN NON-RHABDOMYOSARCOMA SOFT TISSUE SARCOMAS (ARST1321): A REPORT OF MAJOR WOUND COMPLICATIONS FROM THE CHILDREN'S ONCOLOGY GROUP AND NRG ONCOLOGY

Mark L. Kayton, MD,
Department of Surgery, K. Hovnanian Children's Hospital at Jersey Shore University Medical Center, Hackensack-Meridian Health Network, Neptune, NJ

Aaron R. Weiss, DO,
Department of Pediatrics, Maine Medical Center, Portland, ME

Wei Xue, PhD,
Department of Biostatistics, University of Florida, Gainesville, FL

Odion Binitie, MD,
Department of Sarcoma, Moffitt Cancer Center, Tampa, FL

Andrea Hayes, MD,
Department of Surgery, Howard University, Washington, DC

R. Lor Randall, MD,
Department of Orthopaedic Surgery, University of California Davis, Sacramento, CA

Joel I. Sorger, MD,
Department of Orthopedic Surgery, Cincinnati Children's Hospital, Cincinnati, OH

Douglas S. Hawkins, MD,
Department of Pediatrics, University of Washington School of Medicine and Seattle Children's Hospital, Seattle, WA

Sheri L. Spunt, MD, MBA,
Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA

Dian Wang, MD, PhD,
Department of Radiation Oncology, Rush University Medical Center, Chicago, IL

Lynn Million, MD,
Department of Radiation Oncology, Stanford University School of Medicine, Palo Alto, CA

Stephanie Terezakis, MD,

Corresponding author: Mark L. Kayton, MD, Department of Surgery, K. Hovnanian Children's Hospital at Jersey Shore University Medical Center, Hackensack-Meridian Health Network, 19 Davis Avenue, Hope Tower – 4th Floor, Neptune, NJ 07753; Tel.: (732) 935-0407; Fax: (732) 935-0757; mark.kayton@hmhn.org.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

All other co-authors have no relevant disclosures.

Department of Radiation Oncology, University of Minnesota, Masonic Cancer Center, Minneapolis, MN

Edwin Choy, MD, PhD,
Department of Medical Oncology, Massachusetts General Hospital, Boston, MA

Scott H. Okuno, MD,
Department of Oncology, Mayo Clinic, Rochester, MN

Rajkumar Venkatramani, MD, MS, MBA,
Department of Pediatrics, Texas Children's Cancer Center, Texas Children's Hospital, Baylor College of Medicine, Houston, TX

Yen-Lin Chen, MD,
Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA

Thomas J. Scharschmidt, MD
Department of Orthopaedics, James Cancer Hospital and Nationwide Children's Hospital, Columbus, OH

Abstract

Background and objectives: The impact upon wound healing of targeted molecular therapies, when incorporated into neoadjuvant therapy of soft tissue sarcoma, is largely unknown. Here, we describe wound complications following addition of pazopanib, a tyrosine kinase inhibitor (TKI), to neoadjuvant radiotherapy (RT) +/− chemotherapy for soft tissue sarcoma.

Methods: Wound complications were evaluated on dose-finding and randomized arms of ARST1321, a phase II/III study incorporating neoadjuvant RT, +/− pazopanib, +/− ifosfamide/doxorubicin (ID) for sarcoma therapy.

Results: Of 85 evaluable patients, 35 (41%) experienced postoperative wound complications. Most (57%) were grade III. Randomization to pazopanib+RT+ID carried a 50% wound complication rate (17/34, with 47% grade III), compared to 22% (5/23) with ID+RT alone. In non-chemotherapy study arms, pazopanib+RT resulted in a 59% wound complication rate versus 25% for those receiving RT alone. Grade III wound complications occurred among 26% (15/58) of all patients receiving pazopanib. Wound complications occurred a median of 35 days postoperatively. Some occurred following diagnostic biopsies and at remote surgical sites.

Conclusion: The addition of pazopanib to neoadjuvant chemotherapy and RT resulted in a higher wound complication rate following therapy of soft tissue sarcoma. The rate of grade III complications remained comparable to that reported in contemporary literature.

Keywords

wound healing; wound complications; sarcoma; neoadjuvant; pazopanib

Introduction

Soft tissue sarcomas (STS) represent a rare, heterogenous group of aggressive tumors with over 40 different histologic subtypes. The majority of these subtypes have historically been

treated similarly regardless of their specific histology. The treatment for high-grade STS is predominantly wide surgical resection up front, or after neoadjuvant chemoradiotherapy for unresectable disease, with or without adjuvant radiotherapy; chemotherapy is generally reserved for neoadjuvant treatment in the case of unresectable disease, or in the setting of more chemoresponsive histologies among patients at high risk for the development of distant metastases. Preoperative radiation has been shown to improve rates of local control, to decrease the total dose of RT required, and to be associated with improved survival [1–3]. However, the use of preoperative radiation is also associated with an increased rate of wound complications, which in contemporary reports remain in the range of 22% to 35% [2,4–7].

Given the poor 5-year survival associated with large, high-grade sarcomas, many published trials have explored the use of chemotherapy in order to improve outcomes [8]. Response to neoadjuvant chemotherapy yields a survival benefit for initially unresected pediatric nonrhabdomyosarcoma soft tissue sarcoma (NRSTS), with the best outcomes occurring among those able to undergo delayed complete resection [9]. Prior studies from the Children's Oncology Group (COG) have shown that the administration of neoadjuvant chemoradiation enables delayed R0/R1 resection among a large majority of risk-stratified pediatric patients with unresected NRSTS, achieving equivalent outcomes to those resected up front while permitting administration of lower overall radiotherapy doses [10,11]. Still, studies in adult patients have reported wound complication rates of 10% to 30% following neoadjuvant chemoradiation therapy [12]. Most such studies have utilized traditional cytotoxic chemotherapy agents, including ifosfamide and doxorubicin (ID).

Recently, agents that target the multiple signaling pathways involved in tumorigenesis across STS subtypes have been explored to enhance the effects of traditional cytotoxic chemotherapy. The Vascular Endothelial Growth Factor (VEGF) Receptor, Platelet Derived Growth Factor Receptor, and c-Kit pathways are among the most commonly dysregulated in STS [13]. The multi-targeted TKI, pazopanib, a potent inhibitor of these pathways, improved outcomes in adults with advanced STS, and is approved by the United States Food and Drug Administration for therapy of adults with advanced STS [14]. Preclinical studies have demonstrated a potential synergistic interaction between pazopanib and conventional cytotoxic chemotherapy [15,16]. A limited number of clinical trials in STS combining pazopanib and cytotoxic chemotherapy have been conducted [17,18]. However, TKIs and other targeted agents of the VEGF pathway have been associated with wound complications and delays in wound healing. The TKI, apatinib, demonstrated an 11% grade 3+ wound complication rate in patients with advanced sarcoma; and a previous trial evaluating the VEGFR inhibitor, bevacizumab, in combination with pre-operative RT in STS, reported a 20% rate of major wound complications [19,20].

ARST1321 was a phase II/III study in select high-grade soft tissue sarcomas evaluating the TKI pazopanib with radiation +/− ID chemotherapy followed by delayed tumor resection in both pediatric and adult patients. The objective of this report is to detail the major wound complications observed with this protocol.

Materials and Methods

Study Design and Participants

ARST1321 was an open-label, phase II/III, randomized clinical trial conducted jointly by the Children's Oncology Group and NRG Oncology as part of the National Cancer Institute Clinical Trials Network (NCTN) (NSC# 737754, IND# 118613). Accrual was drawn from multiple National Cancer Institute-supported cooperative groups. Collaboration between adult groups and COG enabled the participation of adult patients as well as children age 2 or older. Other eligibility criteria have been detailed elsewhere [21].

Patients with newly diagnosed, potentially resectable (but initially unresected) non-rhabdomyosarcoma soft tissue sarcomas of the extremity and trunk were enrolled onto either a "chemotherapy" cohort or a "non-chemotherapy" cohort. The chemotherapy cohort was open to patients with tumors over 5 cm in size, of grade 2 or 3 by the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system, with the following histologies: synovial sarcoma, angiosarcoma, adult fibrosarcoma, mesenchymal chondrosarcoma, leiomyosarcoma, liposarcoma (excluding myxoid liposarcoma), undifferentiated pleomorphic sarcoma, embryonal sarcoma of the liver, and unclassified STS too undifferentiated to be placed in a specific pathologic category.

The non-chemotherapy cohort was open to patients with grade 2 or 3 tumors of any size, of the remaining non-rhabdomyosarcoma histologies adopted from the 2013 World Health Organization Classification of STS, intermediate (rarely metastasizing) and malignant tumors [22].

The trial was approved by the Pediatric Central Institutional Review Board of the National Cancer Institute and by the institutional review boards of each participating institution, as required. Procedures followed were in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 1983, and informed consent was obtained from each patient or parent/guardian (with patient assent as appropriate).

Procedures—In an initial, nonrandomized phase of this trial, we assessed dose-limiting toxicities for children and adults receiving pazopanib in combination with chemoradiotherapy or with RT [23]. Once dose levels were established to carry forward into the randomized portion of the study, subsequent patients eligible for the chemotherapy cohort were randomized to neoadjuvant therapy with ID and 45 Gy RT at 1.8 Gy per fraction starting at Week 4 with (Regimen A) or without (Regimen B) concurrent pazopanib at a daily dose of 350 mg/m^2 for pediatric patients and 600 mg for adults. Surgical resection was performed at Week 13. Patients receiving pazopanib had the drug discontinued for at least seven days prior to surgery. Postoperative continuation of the assigned therapy resumed at Week 16. Completeness of surgical resection was determined by review of pathology reports. R0 resection was defined as microscopic absence of tumor on the inked margins regardless of the proximity of tumor cells to the margin. For patients with gross residual disease (R2 resection), a postoperative boost of 21.6 Gy at 1.8 Gy per fraction RT was required (cumulative dose 66.6 Gy).For patients with involved microscopic margins (R1

resection), postoperative boost RT of 16.2 Gy at 1.8 Gy per fraction (cumulative dose 61.2 Gy) was highly recommended but ultimately at the discretion of the treating physician.

Patients enrolled in the non-chemotherapy cohort, subsequent to the dose-finding phase, were randomized to preoperative 50 Gy RT at 2 Gy per fraction with (Regimen C) or without (Regimen D) pazopanib at daily doses of 450 mg/m^2 for pediatric patients and 800 mg for adult patients. Pazopanib, for those patients receiving it, began concurrently with RT at Week 1. Preoperative RT was completed by the end of Week 5. Definitive surgery was performed at Week 10. Patients receiving pazopanib had the drug discontinued for at least seven days prior to surgery, with postoperative resumption of pazopanib at Week 13. For patients with R2 resection, postoperative boost RT to a dose of 20 Gy at 2 Gy per fraction was required (cumulative dose 70 Gy). For patients with R1 resections, postoperative boost RT at a dose of 16 Gy at 2 Gy per fraction (cumulative dose 66 Gy) was highly recommended but optional based on the discretion of the treating physician. Postoperative boost RT was administered once the wound had adequately healed (starting 3 weeks after surgery).

Adverse event reporting:

Standard adverse events were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) versions 4.0 and 5.0 (amendment to update version in 7/2018). In addition to standard adverse event reporting, the following gradable protocol-defined targeted toxicities were explicitly monitored: wound complications, hypertension, cardiotoxicity, dermatitis, gastrointestinal toxicity, and nephrotoxicity.

For wound complication reporting, we amended the protocol to require submission of a wound Central Review Form (CRF) incorporating the Dindo-Clavien scale [24], and characterization of the complication as proposed by O'Sullivan et al. [2], in order to better differentiate among patients requiring interventions for wound-related adverse events (Table 1). We also required submission of any wound-related operative or procedure reports including reports of interventional radiology procedures.

Each case was reviewed by 1 or more of 5 surgeon reviewers on the study committee. Documentation was reconciled between CTCAE and wound CRFs. Wound complications and their treatment were graded according to the Dindo-Clavien scale and categorized based upon our review of protocol-specified data fields completed by treating institutions, as well as submitted operative and pathology reports. Comparisons of wound complications between regimens was conducted using Fisher Exact test or two-sample median test. We did not adjust for confounding.

Results

ARST1321 was opened for patient enrollment on July 7, 2014. In 2018 the Data Safety Monitoring Committee, based upon the planned second interim analysis, recommended halting further accrual because the efficacy threshold with pazopanib was achieved; therefore, accrual was stopped on October 1, 2018. We report the data from this trial based on all available information (approximately 2 years after end accrual date). Eighty-five

patients were eligible for analysis of post-resection, surgical site wound complications, as defined by having adequate surgical and wound complication data submitted for surgical study committee review. Patient characteristics are summarized in Table 2 and a study consort diagram is provided in Figure 1. The most common histologies were synovial sarcoma and undifferentiated pleomorphic sarcoma. Although the majority of patients were ≥ 18 years (66%), the entire age spectrum was well represented and all NCTN cooperative groups contributed to enrollment.

Of the 85 evaluable patients, 77 were on the dose-finding (n=20) or chemotherapy (n=57) arms, and 8 on the non-chemotherapy arm. Overall, 35/85 (41%) had documented resection-site wound complications, which are summarized by regimen in Table 3. The median time from surgery to the wound complication was 35 days (range 0–220 days). Among those randomized to receive pazopanib who had a wound complication, 82% had a delay in treatment (Table 3).

When stratified by Dindo-Clavien grade, there were 10 grade I, 5 grade II, and 20 grade III wound complications. The majority of post resection wound complications were grade III and all of these cases required repeat operative procedures (Table 4). Chemotherapy-associated wound complications [Regimen A (pazopanib + RT + ID) or Regimen B (RT + ID)] are summarized in Table 5. Adding pazopanib to ID+RT (Regimen A) was associated with a 50% (17/34) rate of wound complications (95% CI: 37.1%, 62.9%) compared to 22% (5/23) with ID+RT only (Regimen B) (95% CI: 11.1%, 32.6%) (p=0.0315). The rate of grade III wound complications for patients on Regimen A was 24% (8/34) (95% CI: 12.6%, 34.4%) and the rate of grade III wound complications for patients on Regimen B was 17% (4/23) (95% CI: 7.6%, 27.1%). There were too few randomized patients with RT +/− pazopanib (n=8) to assess the relative effect upon wound complications of randomization to receive pazopanib. However, our dose-finding phase included 13 patients receiving RT + pazopanib, and when these patients are evaluated together with those randomized to receive RT +/− pazopanib, there was a higher rate of wound complications among those receiving RT with pazopanib (10/17, or 59%) compared with those who received RT without pazopanib (1/4 or 25%), although not statistically significant (p=0.3108). The overall rate of grade III wound complications for all patients who received pazopanib was 26% (15/58) (95% CI: 14.6%, 37.1%). The overall rate of grade III wound complications for patients not receiving pazopanib was 19% (5/27) (95% CI: 18.5%, 28.5%).

Tumor site

The majority of patients in this study had extremity tumors, with the lower extremity representing the most common site (61/85 patients overall, 72%). Of the 35 wound complications, 31 (88%) occurred in the lower extremity, 2 (6%) occurred in the upper extremity, and 2 (6%) occurred in the trunk.

Patient age

There were no differences between wound complication rates among pediatric (12/29 or 41%) versus adult patients (23/46 or 41%). Distribution of wound complications among young, middle-aged and older adults did not show any relevant differences (Table 6).

Advanced wound closure adjuncts

Fifteen of the 85 evaluable patients had advanced wound closure adjuncts performed at the index resection. This included 11 flaps and 4 grafts (skin graft or biologic matrix). Among those patients undergoing advanced wound closure adjuncts, 6/15 (40%) had wound complications, of which 1 was grade I, 1 was grade II, and 4 were grade III. These 6 patients were distributed among the dose-finding phase receiving pazopanib and RT (n=1), Group A (chemo-RT + pazopanib, n=3) and Group B (chemo-RT without pazopanib, n=2).

Biopsy site wound complications

Five patients (two from Dose-Finding RT arm, and three from Regimen A) among the 124 study-eligible enrollees were determined to have wound complications associated with the initial biopsy procedure at enrollment, prior to definitive surgical resection of their tumors. All 5 of these patients received pazopanib. Of these, 2 were incisional biopsies. One of these 2 experienced a wound dehiscence that resulted in the patient coming off protocol therapy and the other was a wound infection that did not delay therapy. The remaining 3, all of which were core biopsies, were able to go on to primary site surgery.

Non-sarcoma-site wound complications

Three patients had wound complications at sites distant from their sarcoma. Two of these patients had dehiscence at the site of their venous access ports. One of these two came off study prior to definitive sarcoma surgery (for withdrawal of consent), and the other went on to complete protocol therapy. The third distant-site wound complication merits discussion owing to the unusual series of events. The patient, a 67-year-old woman with a myxofibrosarcoma of the thigh, received induction therapy including pazopanib (regimen A). She developed a skin infection, then pseudomonas bacteremia, followed by dehiscence of a surgical wound from an abdominal hysterectomy—which had been performed 15 years previously. The hysterectomy wound required surgical debridement and repair. The patient withdrew from protocol therapy.

Discussion

This prospective phase II/III randomized study achieved one of its key primary endpoints, showing that the addition of pazopanib to RT or combination chemoradiotherapy improved pathologic response among children and adults with large, unresected, intermediate- or high-grade chemosensitive STS [21]. While pathologic response may predict improved outcome in STS, improvements in pathologic response must be counterbalanced against potential complications of TKIs. This study was designed with the recognition that, among such complications, the incidence and characteristics of wound complications would occupy an important role. We found that pazopanib, in combination with ID + RT, led to a higher incidence of wound complications than did ID + RT alone. Encouragingly, despite this higher incidence, the rate of major (grade III) wound complications was 24% (8/34) among patients randomized to receive pazopanib with chemoradiotherapy, and 26% (15/58) among patients receiving pazopanib on all study arms.

This study relied on several reporting mechanisms to collect complete data on wound complications following tumor biopsies, following vascular access procedures, as well as those following definitive surgical resection. Information was also collected on the interventions required to treat wound complications, delays in therapy, as well as other wound related morbidity and mortality. Study team reviewers made use of the Clavien-Dindo scale for the grading of surgical complications. This scale, used in numerous published studies, is based upon the level of intervention required to manage a complication, rather than upon a subjective opinion as to the severity of the complication [25]. It has been reported to have a high degree of interobserver reliability [25] and has been applied in a variety of surgical specialties [26, 27] including surgical oncology. For instance, among colorectal cancer patients suffering complications, the postoperative Clavien-Dindo grade correlated with decreased overall survival, disease free survival, and cancer specific survival, as well as with overall recurrence rates [28].

Wound complications were of particular concern in the pazopanib treatment arms given the known toxicity of TKIs. The overall grade III wound complication rate observed in our study (24%) was found to be within the accepted historical rate (up to 30%) for patients receiving neoadjuvant chemoradiotherapy without the addition of a TKI [29]. The 24% incidence of grade III complications is of particular interest since these required intervention, typically operative intervention. These patients also had delays in resuming systemic treatment following surgical resection.

Historical data on wound complication rates

Numerous prior studies have reported the effects of preoperative radiation on wound healing. In 2002, O'Sullivan et al. compared pre- versus post-operative RT in the treatment of extremity sarcomas. Their preoperative RT cohort had a 35% incidence of wound complications [2]. DeLaney et al., in 2003 reported a 29% incidence of acute wound complications among 48 patients treated with preoperative chemoradiation in high grade STS [29]. A report by Tseng from the MD Anderson Radiation Oncology database reviewed a series of 173 patients with extremity sarcoma and reported a 32% rate of major wound complications with preoperative RT followed by surgery [4]. This incidence of approximately 30% has recently been corroborated in multiple other studies [5,7]. While the terminology found in this literature has varied (wound complications, acute wound complications, and major wound complications), the studies by O'Sullivan, DeLaney and Tseng, in particular, defined such wound events as including secondary operations, invasive procedures, readmission, or persistent need for deep packing changes; therefore, these are closely comparable to the criteria for grade III wound complications used in the present study.

Timing of wound complications

The half-life of pazopanib is approximately 31 hours, which must be considered in the setting of surgical planning. Allowing the drug to clear in the perioperative period might theoretically assist with wound healing. All patients were off systemic treatment for approximately 7 days prior to and 14 days after surgery. The rationale for these time-frames was based off data from other TKIs used in the perioperative setting and the half-life of

pazopanib. If there was evidence of delayed wound healing after surgery, systemic treatment was held for up to an additional 2 weeks. We evaluated wound complications as they related to the time from surgery and found that the median time from surgery to recognition of a wound complication was 35 days. The longest was 220 days postoperatively. In many patients, therefore, wound complications were identified only after planned postoperative therapy had already resumed.

Haas et al., in a phase I feasibility study of 12 patients receiving neoadjuvant therapy using radiation and pazopanib, reported 2 wound complications among the 10 patients undergoing operation (20% wound complication rate) in the 21-day window following surgery, with pazopanib held for 5–7 weeks prior to surgery [30]. In a phase I trial using the TKI inhibitor sorafenib combined with radiotherapy for STS, Canter et al. reported grade III surgical site complications in 3 out of 8 patients (38%), with surgical resection occurring 4–6 weeks after discontinuation of the drug [31]. In light of the findings of these as well as the present study, the perioperative management of TKIs should take into account the half life and pharmacodynamic characteristics of the agent. Additionally, recognition of the risk of late wound complications should be factored into the care of patients whose therapy includes the use of TKIs.

Tumor site

Site of primary tumor has a known impact on wound complications. In general, tumors seated in deep locations and the proximal thigh/groin locations are associated with a greater rate of wound complications, approaching 50% with pre-operative RT [2]. So although lower extremity location made up the majority of patients in the present study (61/85, or 72%), patients with lower extremity tumors exhibited a disproportionate incidence of wound complications (31/35, or 89%, Table 2). Unfortunately, the numbers were too small to draw any significant conclusions regarding the merits of different closure techniques in this study, although further prospective studies would help to better elucidate variables that may influence wound complication rates in the lower extremity.

Patient age

Overall, the type and frequency of toxicities were generally similar for pediatric and adult patients. Although it is sometimes said that pediatric (<18 years of age) patients tolerate systemic agents better and have lower complications when compared to their adult counterparts, one of the advantages of performing a study that incorporates the entire age spectrum is the unique opportunity to compare toxicities directly among children and adults with uniformly delivered therapy. Our finding that toxicities were similar across the age spectrum suggests that age is not an absolute determinant for consideration of this therapy approach. Pediatric patients and adult patients in this study had uniform wound complication rates of 41%. A recent review of the American College of Surgeons National Surgical Quality Improvement Project-Pediatrics (NSQIP-P) evaluated complications in 192 pediatric bone and soft tissue sarcoma patients and found that deep wound dehiscence occurred in only 1% of patients [32] None of the soft tissue sarcoma patients in their review (n=54) experienced a deep wound complication. However, they did note that their pediatric cohort had a higher 30-day combined wound dehiscence plus surgical site infection rate (7.8%)

versus an adult cohort reported in a paired study (5.6%), although this did not lend itself to statistical comparison. The authors suggested this was related to a more aggressive approach to resuming chemotherapy after surgery in pediatric sarcomas.

Our finding of three non-sarcoma site wound complications highlights another important point. We observed two wound complications in port sites and one in a remote surgical incision. These findings suggest that all current and previous surgical sites should be kept under active surveillance for potential wound complication while undergoing treatment with pazopanib and potentially other TKIs.

We recognize that in addition to making use of wound CRFs as data collection instruments, our analysis of the nature and severity of wound-related interventions was aided by direct review of submitted operative reports, including those related to planned sarcoma resection as well as those related to surgical therapy of wound complications. We identified at least 6 instances in which a brief communication indicated to the study team that there may have been a wound event (e.g., an isolated box checked “yes” on a study form; an email or other communication), but no corroborating operative reports or wound CRFs were provided to substantiate or characterize the possible event. Therefore, the present report may slightly understate the true incidence of wound complications.

Additionally, we recognize that accrual of patients to this study was halted based upon a planned interim analysis by the Data Safety Monitoring Committee, once a primary study endpoint (rate of pathologic tumor response) was reached. This in turn may have limited the ability to assess confounding factors or to detect significant differences in wound complications among treatment groups.

In summary, the overall rate of wound complications observed in this study was 41%. The major wound complication (grade III) rate was 24%. Most wound complications occurred in the lower extremity. Pazopanib, when combined with chemotherapy and RT, led to a higher wound complication rate compared to chemoradiotherapy and to RT alone in patients with advanced STS. Despite this increased risk with pazopanib, the major wound complication rate with pazopanib is similar to previously reported rates seen with preoperative RT with or without other agents. Future reports will evaluate whether the risks associated with pazopanib translate to differences in overall and event-free survival among patients with nonrhabdomyosarcoma soft tissue sarcoma.

Conclusions

Grade III wound complications occurred among 26% (15/58) of all patients receiving pazopanib, at a median of 35 days postoperatively, and were seen equally in pediatric and adult patients. While the grade III wound complication rate remained comparable to that seen in other published reports following multimodal therapy for soft tissue sarcoma, the addition of pazopanib was associated with an increased rate of wound complications among patients receiving neoadjuvant chemoradiotherapy as well as among those receiving preoperative radiotherapy without chemotherapy.

Acknowledgments

The authors acknowledge the contributions of Robin Arens, AAS, Clinical Research Associate; and of Research Coordinators Justin Davis and Ellen Tsan, MPH.

Funding Sources

This study was funded by National Clinical Trials Network Operations Center Grant U10CA180886, National Clinical Trials Network Statistics & Data Center Grant U10CA180899, National Cancer Institute IROC Operations Grant CA180803, St. Baldrick's Foundation and Seattle Children's Foundation, from Kat's Crew Guild through the Sarcoma Research Fund.

Disclosures

MLK is a co-inventor on US patents 5641867, 6228837, 6734168, 9125959, 9339574, and 9839709, none of which are directly related to this work or are currently under licensure. ARW is on the medical advisory board of SpringWorks Therapeutics with reimbursement for travel and lodging only, no honoraria; and is a member of the data safety monitoring committee and paid consultant for BioAtla. DSH reports grants and non-financial support from Loxo Oncology, Bayer, and Bristol Myers Squibb; non-financial support from AstraZeneca and Celgene; and grants from Merck Sharpe & Dohme, Lilly, Eisai, Glaxo Smith Kline, Novartis, Sanofi, Amgen, Seattle Genetics, Jazz Pharmaceuticals, and Incyte, outside the submitted work. SLS reports grants from National Cancer Institute and Children's Oncology Group, during the study and grants from F Hoffman-La Roche, Novartis, Alex's Lemonade Stand Foundation, Cookies for Kids' Cancer, Bayer, Sanofi, Loxo Oncology, Incyte Corporation, Bristol Myers Squibb, St Baldrick's Foundation, Pfizer, and University of California, Santa Cruz, outside the submitted work. EC reports a grant from Novartis during the study. TJS reports personal fees from Stryker Orthopedics and Daiichi-Sanko, outside the submitted work.

Abbreviations and acronyms

TKI	tyrosine kinase inhibitor
RT	radiotherapy
ID	ifosfamide/doxorubicin
STS	soft tissue sarcomas
NRSTS	non-rhabdomyosarcoma soft tissue sarcoma
COG	Children's Oncology Group
VEGF	Vascular Endothelial Growth Factor
NCTN	National Clinical Trials Network
FNCLCC	Fédération Nationale des Centres de Lutte Contre le Cancer
CTCAE	Common Terminology Criteria for Adverse Events
CRF	Central Review Form
NSQIP-P	American College of Surgeons National Surgical Quality Improvement Project-Pediatrics

References

1. Haas RL, Delaney TF, O'Sullivan B, et al. : Radiotherapy for management of extremity soft tissue sarcomas: why, when, and where? Int J Radiat Oncol Biol Phys 2012 Nov 1;84(3):572–580. [PubMed: 22520481]

2. O'Sullivan B, Davis AM, Turcotte R, et al. : Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. Lancet 2002 Jun 29;359(9325):2235–2241. [PubMed: 12103287]

3. Koshy M, Rich SE, Mohiuddin MM: Improved survival with radiation therapy in high-grade soft tissue sarcomas of the extremities: a SEER analysis. Int J Radiat Oncol Biol Phys 2010 May 1;77(1):203–209. [PubMed: 19679403]

4. Tseng JF, Ballo MT, Langstein HN, et al. : The effect of preoperative radiotherapy and reconstructive surgery on wound complications after resection of extremity soft-tissue sarcomas. Ann Surg Oncol 2006 Sep;13(9):1209–1215. [PubMed: 16952046]

5. Cannon CP, Ballo MT, Zagars GK, et al. : Complications of combined modality treatment of primary lower extremity soft-tissue sarcomas. Cancer 2006 Nov 15;107(10):2455–2461. [PubMed: 17036354]

6. Moore J, Isler M, Barry J, Mottard S: Major wound complication risk factors following soft tissue sarcoma resection. Eur J Surg Oncol 2014 Dec;40(12):1671–1676. [PubMed: 25456440]

7. Griffin AM, Dickie CI, Catton CN, et al. : The influence of time interval between preoperative radiation and surgical resection on the development of wound healing complications in extremity soft tissue sarcoma. Ann Surg Oncol 2015 Sep;22(9):2824–2830. [PubMed: 26018726]

8. Pervaiz N, Colterjohn N, Farrokhyar F, et al. : A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer 2008 Aug 1;113(3):573–581. [PubMed: 18521899]

9. Ferrari A, Miceli R, Rey A, et al. : Non-metastatic unresected paediatric non-rhabdomyosarcoma soft tissue sarcomas: Results of a pooled analysis from United States and European groups. Eur J Cancer 2011 March;47(5):724–731. [PubMed: 21145727]

10. Spunt SL, Million L, Chi Y-Y, et al. : Prospective analysis of a risk-based treatment strategy for non-rhabdomyosarcoma soft tissue sarcomas in patients under 30 years of age: a report from Children's Oncology Group study ARST0332. Lancet Oncol 2020 Jan;21(1):145–161. [PubMed: 31786124]

11. Million L, Hayes-Jordan A, Chi Y-Y, et al. : Local control for high-grade nonrhabdomyosarcoma soft tissue sarcoma assigned to radiation therapy on ARST0332: a report from the Childrens Oncology Group. Int J Radiation Oncol Biol Phys 2021;110(3):821–830.

12. Rivard JD, Puloski SS, Temple WJ, et al. : Quality of life, functional outcomes, and wound complications in patients with soft tissue sarcomas treated with preoperative chemoradiation: a prospective study. Ann Surg Oncol 2015 Sep;22(9):2869–2875. [PubMed: 25783679]

13. Le Tourneau C, Faivre S, Raymond E: New developments in multitargeted therapy for patients with solid tumours. Cancer Treat Rev 2008 Feb;34(1):37–48. [PubMed: 17983706]

14. van der Graaf WT, Blay JY, Chawla SP, et al. ; EORTC Soft Tissue and Bone Sarcoma Group; PALETTE study group: Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012 May 19;379(9829):1879–1886. [PubMed: 22595799]

15. Hashimoto K, Man S, Xu P, et al. : Potent preclinical impact of metronomic low-dose oral topotecan combined with the antiangiogenic drug pazopanib for the treatment of ovarian cancer. Mol Cancer Ther 2010 Apr;9(4):996–1006. [PubMed: 20371722]

16. Li Y, Yang X, Su LJ, Flaig TW: Pazopanib synergizes with docetaxel in the treatment of bladder cancer cells. Urology 2011 Jul;78(1):233.e7–233.e13.

17. Hamberg P, Boers-Sonderen MJ, van der Graaf WT, et al. : Pazopanib exposure decreases as a result of an ifosfamide-dependent drug-drug interaction: results of a phase I study. Br J Cancer 2014 Feb 18;110(4):888–893. [PubMed: 24366297]

18. Munhoz RR, D'Angelo SP, Gounder MM, et al. : A Phase Ib/II Study of Gemcitabine and Docetaxel in Combination With Pazopanib for the Neoadjuvant Treatment of Soft Tissue Sarcomas. Oncologist 2015 Nov;20(11):1245–1246. [PubMed: 26449382]

19. Xie L, Guo W, Wang Y, et al. : Apatinib for advanced sarcoma: results from multiple institutions' off-label use in China. BMC Cancer 2018 Apr 6;18(1):396. [PubMed: 29625604]

20. Yoon SS, Duda DG, Karl DL, et al. : Phase II study of neoadjuvant bevacizumab and radiotherapy for resectable soft tissue sarcomas. Int J Radiat Oncol Biol Phys 2011 Nov 15;81(4):1081–1090. [PubMed: 20932656]
21. Weiss AR, Chen YL, Scharschmidt TJ, et al. : Pathological response in children and adults with large unresected intermediate-grade or high-grade soft tissue sarcoma receiving preoperative chemoradiotherapy with or without pazopanib (ARST1321): a multicentre, randomised, open-label, phase 2 trial. Lancet Oncol 2020 Aug;21(8):1110–1122. [PubMed: 32702309]
22. Fletcher CD, Unni KK, Mertens F (eds). World Health Organization Classification of Tumours, Pathology, and Genetics: Tumours of Soft Tissue and Bone. Lyon: IARC Press, 2013.
23. Chen YL, Weiss AR, Scharschmidt T, et al. : Results of the dose-finding phase of ARST 1321 from the Childrens Oncology Group and NRG Oncology: neoadjuvant chemoradiation or radiation therapy +/− pazopanib in non-rhabo soft tissue sarcomas [abstract]. J Clin Oncol 2019;37 (suppl; abstr 11070).
24. Dindo D, Demartines N, Clavien PA: Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004 Aug;240(2):205–213. [PubMed: 15273542]
25. Clavien PA, Barkun J, de Oliveria ML, et al. : The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250:187–196. [PubMed: 19638912]
26. Sink EL, Leunig M, Zaltz I, et al. : Reliability of a complication classification system for orthopedic surgery. Clin Orthop Relat Res 2012;470:2220–2226. [PubMed: 22528378]
27. Mitropoulos D, Artibani W, Biyani CS, et al. : Validation of the Clavien-Dindo grading system in urology by the European Association of Urology guidelines ad hoc panel. Eur Urol Focus 2018;4(4):608–613. [PubMed: 28753862]
28. Duraes LC, Stocchi L, Steele SR, et al. : The relationship between Clavien-Dindo morbidity classification and oncologic outcomes after colorectal cancer resection. Ann Surg Oncol 2018;25:188–196. [PubMed: 29116488]
29. DeLaney TF, Spiro IJ, Suit HD, et al. : Neoadjuvant chemotherapy and radiotherapy for large extremity soft-tissue sarcomas. Int J Radiat Oncol Biol Phys 2003 Jul 15;56(4):1117–1127. [PubMed: 12829150]
30. Haas RL, Gelderblom H, Sleijfer S, et al. : A phase I study on the combination of neoadjuvant radiotherapy plus pazopanib in patients with locally advanced soft tissue sarcoma of the extremities. Acta Oncol 2015;54(8):1195–1201. [PubMed: 25920360]
31. Canter RJ, Borys D, Olusanya A, et al. : Phase I trial of neoadjuvant conformal radiotherapy plus sorafenib for patients with locally advanced soft tissue sarcoma of the extremity. Ann Surg Oncol 2014 May;21(5):1616–1623. [PubMed: 24554062]
32. Gallaway KE, Ahn J, Callan AK: Thirty-day outcomes following pediatric bone and soft tissue sarcoma surgery: a NSQIP Pediatrics analysis. Sarcoma 2020 Feb 14;2020:1283080.

Synopsis

In this phase II/III, prospective, randomized, collaborative, multi-group clinical trial involving children and adults with soft tissue sarcoma, the addition of the tyrosine kinase inhibitor pazopanib to neoadjuvant chemoradiotherapy or to preoperative radiotherapy was associated with an increased rate of surgical site wound complications. Despite this, the rate of grade III-only wound complications among patients receiving pazopanib on all study arms was 26%, which is in keeping with prior published rates of major sarcoma-site wound infections in the absence of tyrosine kinase inhibitor use. We also observed cases of biopsy-related wound complications and wound events at non-sarcoma surgical sites among those receiving neoadjuvant pazopanib.

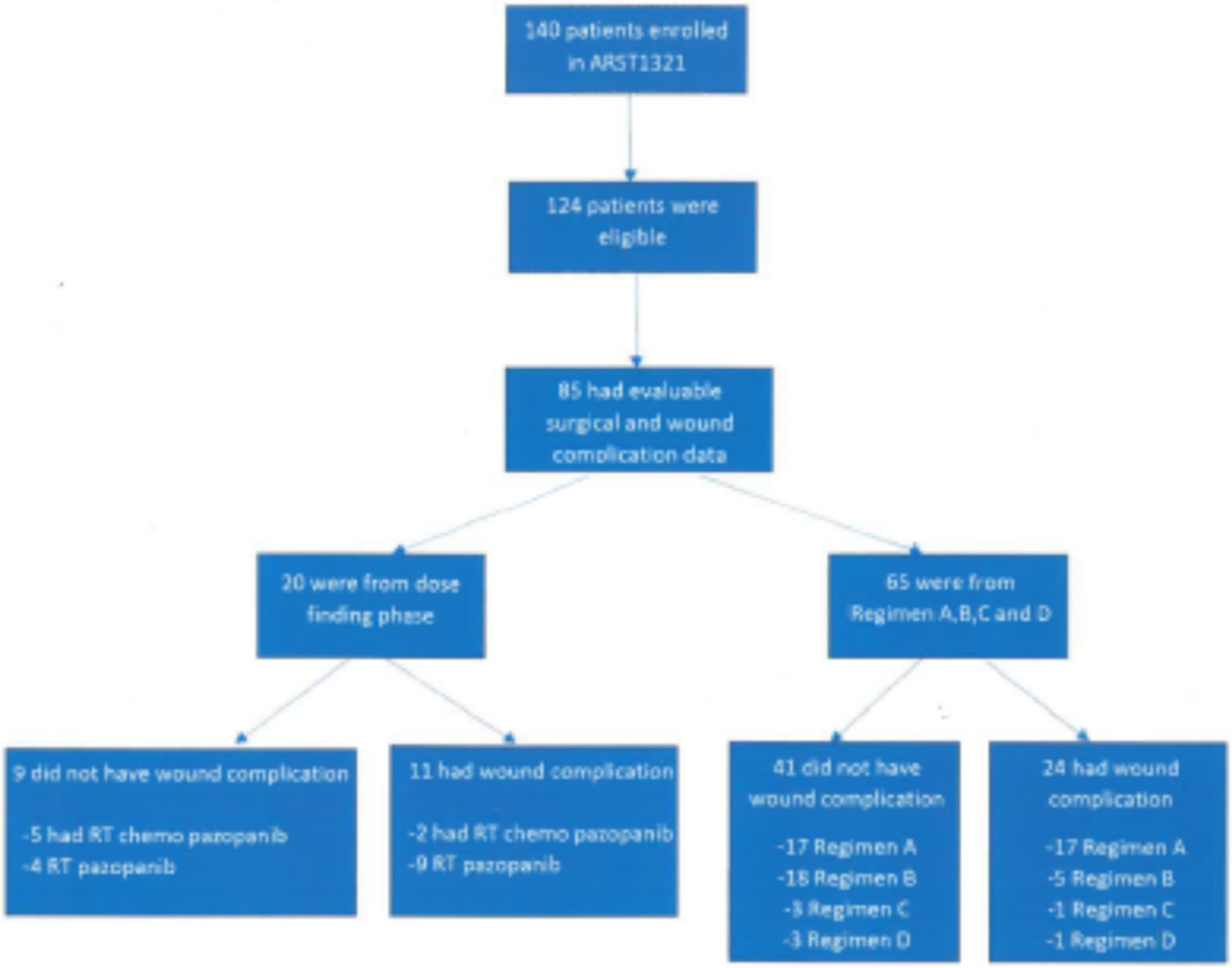

Figure 1.
Consort diagram depicting protocol enrollment, evaluable patients, and distribution of wound complications.

Table 1.

Dindo-Clavien Scale for Wound Complications (adapted with permission* from Dindo et al. 2004 [24])

Grade I	Any deviation from the normal postoperative course without the need for pharmacologic treatment or surgical/endoscopic/ radiological interventions. Includes wound infections opened at bedside. Allowed therapeautic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes., and physiotherapy.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and TPN are included.
Grade III	Requiring surgical, endoscopic or radiologic intervention
IIIa	Not under general anesthesia
IIIb	Under general anesthesia
Grade IV	Life threatening complication requiring ICU management
IVa	Single organ dysfunction (including dialysis)
IVb	Multiorgan dysfunction

Table 2.

Characteristics of eligible patients by wound complication status.

	No Wound Complication (column %) (n=50)	Wound Complication (column %) (n=35)
Treatment		
Dose Finding (RT + chemo + pazopanib)	5 (10.00)	2 (5.71)
Dose Finding (RT + pazopanib)	4 (8.00)	9 (25.71)
Regimen A (RT + chemo + pazopanib)	17 (34.00)	17 (48.57)
Regimen B (RT + chemo)	18 (36.00)	5 (14.29)
Regimen C (RT + pazopanib)	3 (6.00)	1 (2.86)
Regimen D (RT)	3 (6.00)	1 (2.86)
Age		
Median (range)	24.69 (5.87–74.66)	21.37 (5.77–66.48)
< 18 years	17(34.00)	12(34.29)
≥ 18 years	33(66.00)	23(65.71)
Sex		
Male	26 (52.00)	19(54.29)
Female	24 (48.00)	16 (45.29)
Tumor size (cm)		
Median (range)	9.1 (4.20–32.60)	9.7 (3.60–20.60)
Primary site		
Extremity	44 (88.00)	33 (94.29)
Lower Extremity	30 (60.00)	31 (88.00)
Upper Extremity	14 (28.00)	2 (6.00)
Trunk	6 (12.00)	2 (5.72)
T Stage		
T2a	5 (10.00)	4 (11.43)
T2b	38 (76.00)	27 (77.14)
Tx	7 (14.00)	2 (5.71)
Unknown	0	2 (5.71)
N Stage		
N1	4 (8.00)	4 (11.43)
N0	36 (72.00)	27 (77.14)
Nx	10 (20.00)	4 (11.43)
Metastases*		
None	41 (82.00)	25 (71.43)
Lung only	4 (8.00)	8 (22.86)
Other	5 (10.00)	2 (5.71)
Histology		
Synovial sarcoma	20 (40.00)	17 (48.57)
Undifferentiated pleomorphic sarcoma	11 (22.00)	8 (22.86)

	No Wound Complication (column %) (n=50)	Wound Complication (column %) (n=35)
Embryonal sarcoma of the liver	2 (4.00)	0
Leiomyosarcoma	2 (4.00)	2 (5.71)
Other	15 (30.00)	8 (22.86)

RT = radiation therapy, chemo = chemotherapy

Table 3.

Summary of wound complications by treatment arms.

	Dose-Finding Phase (Chemotherapy Cohort, n=2)	Dose-Finding Phase (RT/non-Chemotherapy Cohort, n=9)	Regimen A (RT + chemotherapy + pazopanib, n=17)	Regimen B (RT + chemotherapy, n=5)	Regimen C (RT + pazopanib, n=1)	Regimen D (RT, n=1)
Wound complication grade						
Grade I	1 (50%)	2 (22.22%)	6 (35.29%)	0	1 (100%)	0
Grade II	0	1 (11.11%)	3 (17.65%)	1 (20.00%)	0	0
Grade III (IIIa, IIIb, IIIx)	1 (50%)	6 (66.67%)	8 (47.06%)	4 (80.00%)	0	1 (100%)
Time from surgery to wound complication, Median (range in days)	38.5 (33–44)	32 (0–113)	38 (0–220)	14 (0–70)	28 (28–28)	62 (62–62)
Delay in treatment (>14 days after surgery to restart of chemotherapy)	2 (100%)	6 (66.67%)	14 (82.35%)	2 (40.00%)	1 (100%)	0

RT = radiation therapy

Table 4.

Grade III wound complications and returns to OR

Nature of grade III wound complications	
Secondary operations required for wound treatment	11
Invasive procedures required for wound care	6
Wound infection	1
Wound dehiscence	1
Wound infection and wound dehiscence	1

Returns to OR (“takebacks”) among patients with Grade III wound complications	
0 takebacks	0
1 takeback	14
2 takebacks	0
3 takebacks	1
Unknown or incomplete data	5

Table 5.

Summary of wound complications occurring in patients randomized to receive pazopanib (Regimen A) versus no pazopanib (Regimen B)

	Regimen A (RT + chemotherapy + pazopanib)	**Regimen B (RT + chemotherapy)**	**P-value**
	(n=17)	**(n=5)**	
Wound complication grade			
Grade I	6 (35.29%)	0	0.3208[§]
Grade II	3 (17.65%)	1 (20.00%)	
Grade III (IIIa, IIIb, IIIx)	8 (47.06%)	4 (80.00%)	
Time from surgery to wound complication occurred			
Median (range)	38.00 (0–220)	14 (0–70)	0.6192[¥]
Delay in treatment	14 (82.35%)	2 (40.00%)	0.1005[§]
Removed from protocol therapy	0	0	

RT = radiation therapy

[§]Fisher Exact test was conducted

[¥]Two-sample median test was conducted

Table 6.

Distribution of wound complications by age bracket.

Age	No Wound Complication (column %) (n=50)	Wound Complication (column %) (n=35)
Median (range)	24.69 (5.87–74.66)	21.37 (5.77–66.48)
< 18 years	17(34.0%)	12(34.3%)
>=18 and <40 years	13(26.0%)	10(28.6%)
>=40 and <60 years	12 (24.0%)	9 (25.7%)
>=60 years	8(16.0%)	4(11.4%)