First-Line Aldoxorubicin vs Doxorubicin in Metastatic or Locally Advanced Unresectable Soft-Tissue Sarcoma
A Phase 2b Randomized Clinical Trial

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**IMPORTANCE** Standard therapy for advanced soft-tissue sarcoma has not changed substantially in decades, and patient prognosis remains poor. Aldoxorubicin, a novel albumin-binding prodrug of doxorubicin, showed clinical activity against advanced soft-tissue sarcoma in phase 1 studies.

**OBJECTIVE** To evaluate efficacy and safety of aldoxorubicin vs doxorubicin in patients with advanced soft-tissue sarcoma.

**DESIGN, SETTING, AND PARTICIPANTS** International, multicenter, phase 2b, open-label, randomized study at general community practices, private practices, or institutional practices. Between August 2012 and December 2013, 140 patients with previously untreated locally advanced, unresectable, or metastatic soft-tissue sarcoma were screened.

**INTERVENTIONS** Randomization (2:1) to aldoxorubicin 350 mg/m² (dose equivalent to doxorubicin 260 mg/m²) or doxorubicin 75 mg/m², administered once every 3 weeks for up to 6 cycles.

**MAIN OUTCOMES AND MEASURES** Primary end point was progression-free survival. Secondary end points were 6-month progression-free survival, overall survival, tumor response rate, and safety. All efficacy end points were evaluated by independent and local review.

**RESULTS** A total of 126 patients were randomized, and 123 received aldoxorubicin (n = 83) or doxorubicin (n = 40). Median (range) patient age was 54.0 (21-77 years); 42 (34%) had leiomyosarcoma. By independent review, median progression-free survival was significantly improved (5.6 [95% CI, 3.0-8.1] vs 2.7 [95% CI, 1.6-4.3] months; P = .02) with aldoxorubicin compared with doxorubicin, as was the rate of 6-month progression-free survival (46% and 23%; P = .02). Median overall survival was 15.8 (95% CI, 13.0 to not available) months with aldoxorubicin and 14.3 (95% CI, 8.6-20.6) months with doxorubicin (P = .21). Overall tumor response rate (by Response Evaluation Criteria in Solid Tumors, version 1.1) by independent review was higher with aldoxorubicin than with doxorubicin (25% [20 patients, all partial response] vs 0%). Grade 3 or 4 neutropenia was more frequent with aldoxorubicin than with doxorubicin (25% [20 patients, all partial response] vs 0%). Grade 3 or 4 neutropenia was more frequent with aldoxorubicin than with doxorubicin (25% [20 patients, all partial response] vs 0%). No acute cardiotoxic effects were observed with either treatment, although left ventricular ejection fraction less than 50% occurred in 3 of 40 patients receiving doxorubicin.

**CONCLUSIONS AND RELEVANCE** Single-agent aldoxorubicin therapy showed superior efficacy over doxorubicin by prolonging progression-free survival and improving rates of 6-month progression-free survival and tumor response. Aldoxorubicin therapy exhibited manageable adverse effects, without unexpected events, and without evidence of acute cardiotoxicity. Further investigation of aldoxorubicin therapy in advanced soft-tissue sarcoma is warranted.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT01514188

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Soft-tissue sarcoma comprises a diverse group of malignant neoplasms. At diagnosis, 23% of cases are locally advanced and another 15% are metastatic. First-line treatment for advanced soft-tissue sarcoma includes doxorubicin hydrochloride, alone or in combination with other chemotherapy agents (eg, ifosfamide). The therapeutic benefit of doxorubicin, however, is limited by adverse effects, including mucositis, myelosuppression, and cumulative, dose-dependent cardiotoxic effects. Although the addition of ifosfamide to doxorubicin-based regimens for soft-tissue sarcoma is standard and generally improves response rates and progression-free survival (PFS), overall survival (OS) is not improved and the incidences of grade 3 or 4 myelosuppression, febrile neutropenia, and deaths from adverse events are markedly increased.

Aldoxorubicin (formerly INNO-206), a novel prodrug of doxorubicin, is derivatized at its C-13 keto-position with a thiobinding, pH-sensitive linker (6-maleimidocaprylic acid hydrazide). On bloodstream entry, the linker rapidly and covalently binds primarily to the thiol group of cysteine-34 of endogenous albumin. The albumin-drug conjugate preferentially localizes to the tumor, and in the acidic tumor environment, the doxorubicin is released via cleavage of the acid-labile hydrazine bond between drug and carrier. This novel approach to drug delivery exploits the leaky vasculature and defective lymphatic drainage (enhanced permeability and retention) characteristics of tumor tissues that promote entrapment of macromolecules within tumors, thereby increasing drug uptake and retention.

Of 13 patients with soft-tissue sarcoma treated at the maximum tolerated dose of aldoxorubicin (350 mg/m²) in a phase 1b/2 study, partial response rate was 38% and stable disease rate was 46%. Seven of the 13 patients had previously received an anthracycline. Median PFS and OS for this cohort were 11.3 and 21.7 months, respectively. Myelosuppression was the most frequent adverse event with aldoxorubicin treatment.

This randomized phase 2b study compared the efficacy and safety of first-line treatment with aldoxorubicin vs doxorubicin in patients with advanced soft-tissue sarcoma.

Methods

Study Design
This was a prospective, randomized, open-label, phase 2b study. Between December 21, 2012, and August 1, 2013, patients were enrolled at 31 sites in Australia, Hungary, India, Romania, Russia, Ukraine, and the United States. Patients were randomized 2:1 to receive either aldoxorubicin (350 mg/m²; dose equivalent of 260 mg/m² doxorubicin) or doxorubicin (75 mg/m²). A 2:1 randomization scheme was selected to extend safety information for aldoxorubicin; because the safety and efficacy of doxorubicin are well documented, the doxorubicin arm served to demonstrate patient responses to the drug similar to those evaluated in other studies. The protocol (Supplement 1) was approved by the institutional review board of each study site. This study was conducted in accordance with US Food and Drug Administration regulations, International Conference on Harmonisation Good Clinical Practices guidelines, the principles of the Declaration of Helsinki, and other applicable regulations and guidelines of the locale and country of each study site. Written consent was obtained from each patient by the investigator or subinvestigator before any protocol-specific tests were performed.

Patients
Patients were enrolled by the investigator at the clinical site. Eligible patients were 15 to 80 years of age (US sites) or 18 to 80 years of age (non-US sites) and had locally advanced, unresectable, and/or metastatic soft-tissue sarcoma of intermediate or high grade, Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2, life expectancy greater than 12 weeks (determined by investigator judgement), and disease measurable by Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1). Prior adjuvant or neoadjuvant chemotherapy (including doxorubicin) was allowed if no tumor recurred for at least 12 months since the last measurement. Patients were excluded if they had prior chemotherapy for advanced disease, prior treatment with doxorubicin or pegylated liposomal doxorubicin of more than 3 cycles or greater than 225 mg/m² cumulative dose, palliative surgery or radiation treatment less than 4 weeks before randomization, or exposure to any investigational agent within 30 days of randomization. Patients with evidence or diagnosis of alveolar soft part sarcoma, chondrosarcoma, rhabdomyosarcoma, osteosarcoma, gastrointestinal stromal tumor, dermatofibrosarcoma, Ewing sarcoma, Kaposi sarcoma, mixed mesodermal tumor, clear-cell sarcomas, or unresectable low-grade liposarcomas were excluded, as were patients with ongoing infection, or with either current or past history of clinically significant cardiac events. Race and ethnicity information, based on the participant’s assessment, was recorded to determine whether bias existed in these areas that might explain differences in either efficacy or safety between the 2 arms of the study.

Interventions
Patients received aldoxorubicin 350 mg/m² or doxorubicin 75 mg/m² administered as a 30-minute intravenous infusion on day 1 of each 21-day cycle, for up to 6 cycles. Two additional cycles of treatment were permitted with approval. Supportive care, including administration of antibiotics, blood components, antiemetics, prophylactic colony-stimulating factor, and
erythropoietin was permitted, at investigator discretion. Localized radiotherapy (with approval) was permitted.

Outcomes
The primary end point was PFS, defined as the interval between the date of randomization and the date of documented objective tumor progression or death by any cause, whichever occurred first. Secondary end points included PFS at 6 months, tumor response, and OS (defined as the interval between the date of randomization and the date of death by any cause). Tumor size was measured by computed tomography or magnetic resonance imaging every 6 weeks and as clinically indicated. Tumor response was assessed using RECIST 1.1, based on measurement of both target and nontarget lesions. Progression-free survival and tumor response end points were assessed both by local investigators and by a central independent laboratory (formerly CoreLab Partners, Inc; Princeton, New Jersey; currently BioClinica, Inc; Newtown, Pennsylvania) that received imaging scans with no patient identifiers, clinical information, or treatment assignment information. The OS end point was assessed by local investigators only. Event-driven end points were recorded in days and converted to months by dividing by 30.4 days/mo. Treatment safety, including incidence and severity of adverse events, was fully evaluated by National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Cardiac safety was assessed by electrocardiography at the end of every cycle. Echocardiography or multigated acquisition scan was performed at the end of cycles 2, 4, and 6, at the end of treatment, and during the follow-up period (at 2 months following the end of treatment, then every 3 months thereafter until disease progression or until another therapy was started).

Sample Size
Power calculations and sample size were calculated on the basis of the primary end point (PFS). Published data show that the PFS (time to progression, in some cases) in this population treated with single-agent doxorubicin is approximately 4.4 months by investigator assessment. On the basis of the use of a 2-sided log-rank test at an α = .05 level of significance, a total of 89 events would be required for at least 83% power to detect a PFS of 8.5 months for aldoxorubicin if 105 patients were entered in the study. Assuming a 15-month accrual period and 12-month follow-up, dropout rates of 20% for each treatment arm at the end of the study (month 27), and that dropouts follow the exponential distribution, 70 and 35 patients would be needed in the aldoxorubicin and doxorubicin arms, respectively, to achieve a total of 89 events, using a randomization ratio of 2:1:aldoxorubicin:doxorubicin. As a result of study site interest and increased screening, enrollment was allowed to increase to 126 randomized participants with 123 treated participants eligible for evaluation.

Randomization
A random allocation sequence was generated by INC Research. After providing informed consent, patients were assigned a unique identification number. The investigator accessed an interactive, integrated voice/web response system (IXRS, Almac Group) and the patient was randomly assigned to a treatment arm. Patients in each treatment arm were stratified by baseline ECOG performance status (0 or 1 vs 2) and by prior chemotherapy status (adjuvant or neoadjuvant chemotherapy vs none). The study was open label; treatments were not blinded to patients or investigators but only to independent reviewers at the central laboratory.

Statistical Analyses
Efficacy was assessed in patients who received at least 1 dose of study drug and had at least 1 postbaseline tumor measurement, thus a modified intent-to-treat population. The primary efficacy end point was analyzed using a log-rank test stratified by the initial performance status and participants who had received prior chemotherapy. For the primary treatment comparison, the treatment effect was statistically significant if the 2-sided log rank P < .05. Safety was assessed in patients who received any amount of study drug. Continuous variables were summarized by mean (standard deviation) or median (range). Frequency tables were used to summarize categorical variables. Logistic regression analysis was used to assess the potential effects of patient characteristics on response and toxicity rates. The distributions of time-to-event end points (eg, PFS and OS) were estimated using the Kaplan-Meier method. Comparison of time-to-event end points by important subgroups of participants was made using the log-rank test. Cox (proportional hazards) regression analysis was used to evaluate multivariable predictive models of time-to-event outcomes.

Results
Patients
A total of 140 patients were screened, 126 patients were randomized to aldoxorubicin (n = 86) or doxorubicin (n = 40), and 123 patients were treated (Figure 1). The distribution of patients by country is shown in eTable 1 in Supplement 2. Three patients randomized to aldoxorubicin did not receive treatment because each withdrew consent before receiving the first dose. Median (range) follow-up was 13 (-1 to 31) months in each treatment group. As of data cutoff date (December 15, 2014), 39 (47%) and 26 (65%) of the aldoxorubicin and doxorubicin cohorts, respectively, had died, 30 (36%) and 7 (18%) remained in follow-up for survival, and 14 (17%) and 7 (18%) had terminated the study. Early terminations due to events other than disease progression were uncommon and similar in both groups.

Overall, baseline patient demographic characteristics were similar between treatment groups (Table 1). The most common histopathologic subtype was leiomyosarcoma (42 [34%]). The 2 groups were otherwise balanced in the distribution of soft-tissue sarcoma subtypes. Per protocol, all patients had tumors of intermediate to high grade. Thirteen (11%) patients had prior adjuvant or neoadjuvant chemotherapy; of these, 7 (54%) had received doxorubicin.

Progression-Free and Overall Survival
Median PFS by investigator assessment was 8.3 (95% CI, 6.4-9.7) months for the aldoxorubicin group and 4.6 (95% CI, 2.7-
5.9) months for the doxorubicin group (P < .001) (Figure 2A). Corresponding median PFS by independent assessment was 5.6 (95% CI, 3.0-8.1) and 2.7 (95% CI, 1.6-4.3) months, respectively (P = .02) (Figure 2B). Rates of PFS at 6 months by investigator assessment were 68% for the aldoxorubicin group and 33% for the doxorubicin group (P < .001). Corresponding rates of PFS at 6 months by independent assessment were 46% and 23%, respectively (P = .21; hazard ratio, 0.73 [95% CI, 0.44-1.20]) (Figure 2B). Rates of PFS at 6 months by investigator (P = .14).

**Tumor Response**

Using RECIST 1.1 criteria, overall response rates by investigator assessment were 23% (19 patients) with aldoxorubicin (including 2% [2 patients] complete response) and 5% (2 patients) with doxorubicin (no complete response) (Table 2). Disease control rates were 77% (64 patients) with aldoxorubicin and 68% (27 patients) with doxorubicin. Corresponding overall response rates by independent assessment were 25% (20 patients, all partial response) and 0, respectively (Table 2). Corresponding disease control rates were 62% (50 patients) and 45% (17 patients), respectively.

Among patients evaluable for assessment of tumor shrinkage in the aldoxorubicin group, 50 of 76 (66%) patients by investigator assessment (Figure 3A) and 46 of 73 (63%) patients by independent assessment (Figure 3B) had any amount of tumor shrinkage. In the doxorubicin group, 15 of 34 (44%) patients by investigator assessment (Figure 3C) and 13 of 32 (41%) patients by independent assessment (Figure 3D) had any amount of tumor shrinkage.

**Adverse Events and Cardiac Safety**

The median (range) number of cycles completed was 6 (1-8; 4 patients were permitted to receive up to 8 cycles) in the aldoxorubicin group and 4 (1-6) in the doxorubicin group. The most frequent nonhematologic adverse events (all grades; ≥20% of patients) were stomatitis, fatigue, alopecia, decreased appetite, and vomiting in the aldoxorubicin group, and alopecia and nausea in the doxorubicin group. Adverse events occurring more frequently with
aldoxorubicin than with doxorubicin included nausea (38 [46%] vs 11 [28%]), stomatitis (26 [31%] vs 5 [12%]), fatigue (24 [29%] vs 6 [15%]), decreased appetite (20 [24%] vs 2 [5%]), and vomiting (19 [23%] vs 7 [17%]). Diarrhea occurred more frequently with doxorubicin than with aldoxorubicin (7 [17%] vs 7 [8%]). Adverse events occurring in at least 10% of patients in either treatment group are presented in eTable
2 in Supplement 2.
Overall, 66 patients (80%) in the aldoxorubicin group and 23 patients (58%) in the doxorubicin group had at least 1 adverse event of grade 3 or 4 severity. Serious adverse events are summarized in eTable 3 in Supplement 2. Grade 3 or 4 neutropenia was more frequent with aldoxorubicin than with doxorubicin (24 [29%] vs 5 [12%]). Grade 3 or 4 adverse events occurred more frequently with aldoxorubicin than with doxorubicin, with the exception of anemia (14 [17%] vs 8 [20%]) and febrile neutropenia (12 [14%] vs 7 [18%]), both of which occurred more frequently with doxorubicin than with aldoxorubicin.

Five (6%) patients in the aldoxorubicin group and 3 (8%) patients in the doxorubicin group discontinued study treatment because of an adverse event. Ten patients terminated the study because of death: 6 (7%) in the aldoxorubicin group from disease progression and 4 (10%) in the doxorubicin group from disease progression (n = 2), septic shock (n = 1), and unknown cause (n = 1).

Cardiac events are summarized in Table 4 in Supplement 2. No patient experienced clinically significant abnormal cardiac function, as measured by clinical symptoms, echocardiography, or multigated acquisition scan, during treatment (cycles 2, 4, 6), at the end of treatment, or afterward during the follow-up period (at 2, 5, 8, or 11 months after the end of treatment). Three patients in the doxorubicin group, but none in the aldoxorubicin group, had left ventricular ejection frac-

### Table 2. Best Overall Tumor Responses

<table>
<thead>
<tr>
<th>Patients With Response</th>
<th>Aldoxorubicin Group (n = 83)</th>
<th>Doxorubicin Group (n = 40)</th>
<th>Aldoxorubicin Group (n = 80)*</th>
<th>Doxorubicin Group (n = 38)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>17 (20)</td>
<td>2 (5)</td>
<td>20 (25)</td>
<td>0</td>
</tr>
<tr>
<td>Overall response (CR+PR)</td>
<td>19 (23)</td>
<td>2 (5)</td>
<td>20 (25)</td>
<td>0</td>
</tr>
<tr>
<td>SD</td>
<td>45 (54)</td>
<td>25 (62)</td>
<td>30 (38)</td>
<td>17 (45)</td>
</tr>
<tr>
<td>Disease control (CR+PR+SD)</td>
<td>64 (77)</td>
<td>27 (68)</td>
<td>50 (62)</td>
<td>17 (45)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>13 (16)</td>
<td>11 (28)</td>
<td>24 (30)</td>
<td>17 (45)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>6 (7)</td>
<td>2 (5)</td>
<td>6 (8)</td>
<td>4 (11)</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; PR, partial response; SD, stable disease.

* For 3 patients in the aldoxorubicin group and 2 patients in the doxorubicin group, the independent central laboratory did not identify a measurable lesion at screening.

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tion (LVEF) values that decreased below 50% of institutional reference ranges during the study. The total number of patients who experienced at least a 10% decrease in LVEF values at any cycle of treatment was 9 (12%) in the aldoxorubicin group and 11 (29%) in the doxorubicin group. During the follow-up period, the proportion of patients with at least a 10% decrease in LVEF values ranged from 0% to 11% for the aldoxorubicin group and from 0% to 33% for the doxorubicin group, depending on the time point assessed.

Median serum troponin levels for the aldoxorubicin group were unchanged from baseline during treatment, at the end of treatment, and during the follow-up period (eTable 4 in Supplement 2). For the doxorubicin group, median troponin levels were increased from baseline at cycles 4 and 6, at the end of treatment, and at 2 months after the end of treatment. By 5 months after the end of treatment, median serum troponin levels in the doxorubicin group had returned to baseline values.

Discussion

Aldoxorubicin for first-line treatment of advanced soft-tissue sarcoma showed superior efficacy over doxorubicin that was confirmed by independent, blinded, central radiology laboratory assessment, a level of data review that minimizes certain biases.19,20 Median OS (by investigator assessment) was longer with aldoxorubicin than with doxorubicin for all patients (15.8 vs 14.3 months) and for patients without prior adjuvant or neoadjuvant chemotherapy (15.8 vs 13.8 months), although differences between groups were not statistically significant. This study was not powered to determine differences in OS between treatment groups, so the observed nonsignificantly improved OS with aldoxorubicin requires confirmation in larger, adequately powered studies.

Differences in response rate between independent and investigator reviews, as observed in our study, are not unprecedented. In a phase 3 study of pazopanib hydrochloride vs placebo for second-line or later treatment of metastatic soft-tissue sarcoma, tumor response rates for pazopanib therapy were 6% by independent review and 9% by investigator review.21 Regarding the low response rate for doxorubicin that we observed, published response rates (investigator assessment using World Health Organization criteria22 or RECIST 1.023) for first-line, single-agent doxorubicin (70, 75, or 80 mg/m²) for advanced soft-tissue sarcoma range from 9% to 27%.8,16-18,24-27 The investigator-assessed response rate of 5% for doxorubicin in our study is consistent with the low end of the published range. Moreover, similar rates of tumor shrinkage with doxorubicin were documented by investigator and independent assessment (44% and 41%), suggesting that the application of response criteria was not excessively discrepant.

Grade 3 or 4 neutropenia occurred more frequently with aldoxorubicin than with doxorubicin therapy, but febrile neutropenia did not. Grade 3 or 4 mucositis and nausea and/or vomiting occurred more frequently with aldoxorubicin than with doxorubicin therapy, but those events were not treatment limiting and occurred at only 2 of the 31 study sites. Aldoxorubicin-related adverse events were overall consistent with those known to occur with doxorubicin treatment, generally resolved between cycles of treatment, and did not result in treatment discontinuation or delays in most patients.

The median cumulative dose of aldoxorubicin received in our study was 2100 mg/m² (dose equivalent of 1560 mg/m² doxorubicin), more than 5-fold the median cumulative dose of doxorubicin (300 mg/m²) received, yet there was no evidence of clinically significant decrease in LVEF or reports of congestive heart failure in either study group. Historically, rates of congestive heart failure have ranged from 0.7% to 83% with cumulative doxorubicin doses of 300 to 950 mg/m².4,5 Although an earlier phase 1 study of aldoxorubicin showed that additional treatment cycles were feasible,2 the number of cycles in the present study was capped at 6 (except for 4 participants), which may partially account for the lack of cardiotoxic effects observed. In an ongoing phase 3 study of aldoxorubicin vs investigator’s choice for treatment of patients with advanced soft-tissue sarcoma who have experienced relapse or lack of response to prior chemotherapies, a protocol amendment was made to allow treatment with aldoxorubicin until disease progression or unacceptable toxic effects (NCT02049905). The primary end point of this large, multinational clinical trial is PFS, and OS is a secondary end point.

Our efficacy results were consistent with those of a phase 3 study of doxorubicin plus ifosfamide vs doxorubicin as first-line treatment of advanced soft-tissue sarcoma.8 By investigator assessment, median PFS was 7.4 months with doxorubicin plus ifosfamide and 4.6 months with doxorubicin, median OS was 14.3 and 12.8 months, and overall response rates were 26.4% and 13.6%, respectively. (In our study, by investigator assessment, median PFS was 8.3 months with aldoxorubicin and 4.6 months with doxorubicin, median OS was 15.8 and 14.3 months, and overall response rates were 23% and 5%, respectively.)

The most common grade 3 or 4 adverse events with doxorubicin plus ifosfamide therapy were hematologic events that occurred at higher frequencies, including febrile neutropenia (46%). Notably, patients in the phase 3 study were overall younger (median age, 47 years in the combination group) than patients in our study (median age, 55 years in the aldoxorubicin group).

The results of this study should be interpreted in the context of the limitations of the study design. Specifically, the study is limited by its relatively small size and open-label design, which, by virtue of how the study drugs needed to be administered, could not be blinded. This could have potentially led to bias in how responses and tumor progressions were evaluated, but this situation was controlled by having a blinded central radiology review for response and progression assessment. This approach to avoid bias is uncommon in phase 2 trials, as well as almost all sarcoma phase 3 studies. Imprecision in progression assessment is inherent to studies in which computed tomography scans are taken only every 6 to 12 weeks, and censoring will also contribute to imprecise assessment of end points. Investigator evaluation of nonlaboratory adverse events can also be imprecise and potentially biased on the basis of prior knowledge of a drug’s profile.
To our knowledge, aldoxorubicin is the first single agent to show significant superior activity over doxorubicin without substantially worsening toxicity.

Aldoxorubicin treatment showed no evidence of acute cardiotoxicity even at cumulative doses of doxorubicin-equivalents that were 2- to 4-fold higher than the recommended limit for native doxorubicin (400 to 600 mg/m²). This result raises intriguing possibilities of further augmenting the efficacy of aldoxorubicin by combining it with doxorubicin hydrochloride (NCT01673438), ifosfamide (NCT02235701), or gemcitabine hydrochloride (NCT02235688), or enhancing the efficacy of combination regimens by allowing higher cumulative anthracycline doses. Aldoxorubicin suggests proof of principle that derivatizing an active chemotherapy compound to bind serum albumin can significantly enhance efficacy—without significantly intensifying toxicity.

Conclusions

Aldoxorubicin may be an important therapeutic option for patients with advanced soft-tissue sarcoma, as well as other solid tumor types. In addition to the phase 3 study for soft-tissue sarcoma, aldoxorubicin is currently under investigation in a phase 2b study in small-cell lung cancer, a phase 2 study of glioblastoma, and a pilot study of Kaposi sarcoma.

Role of the Funder/Sponsor: CytRx Corporation collaborated in the design of the study with 5 academic advisors (S.P.C., K.S., K.G., and Shreyaskumar Patel, MD; MD Anderson Cancer Center, Houston, Texas; and Bartosz Chmielowski, MD; University of California Los Angeles). CytRx had no role in the conduct of the study, or collection, management, or analysis of the data. The study was conducted by INC Research (Raleigh, North Carolina), and data collection, management, and statistical analyses were performed by PRA International (Raleigh, North Carolina); both clinical research organizations were contracted by CytRx. CytRx collaborated with clinical study investigators on interpretation of the data. Drs Wieland and Levitt are employees of CytRx and had extensive involvement in all phases of this manuscript.

Additional Contributions: Anna Lau, PhD, and Patricia Segarini, PhD, of Percolation Communications LLC provided medical writing and editorial support, funded by CytRx.

REFERENCES


Aldoxorubicin in Sarcoma
Teaching an Old Drug New Tricks
Rashmi Chugh, MD; Scott M. Schuetze, MD, PhD

Improving the outcomes of patients with sarcoma has been stunted by the dearth of effective drugs in this diverse group of cancers. Some progress has been made over the past 2 decades in identifying new agents with activity in specific sarcomas, such as imatinib mesylate in gastrointestinal stromal tumor and dermatofibrosarcoma protuberans, trabectedin and eribulin mesylate in liposarcoma and leiomyosarcoma, paclitaxel in angiosarcoma, and gemcitabine hydrochloride combinations and pazopanib hydrochloride in soft-tissue sarcomas. Nonetheless, doxorubicin hydrochloride and ifosfamide remain the most active agents across a broad array of sarcoma subtypes. Both cytotoxics yield relatively low single-agent objective response rates approximating 15% and are associated with substantial toxicity. Although the hunt for novel agents with activity in sarcoma continues, increasingly, antineoplastic strategies have involved redesigning the old drugs with a goal of improving the therapeutic index. This is not a new effort; epirubicin hydrochloride, mitoxantrone hydrochloride, and liposomal doxorubicin are earlier examples that were developed into commercial products. Recent efforts in sarcoma have included development of palifosfamide and evosomedib, each of which alleviates much of the neurotoxicity, nephrotoxicity, and urothelial toxicity of ifosfamide.

The efficacy of doxorubicin therapy could potentially be increased if higher doses could safely be given, but severe myelosuppression, mucositis, and increased cardiac toxic effects occur when doses greater than 75 mg/m² per cycle are administered. In this regard, the study of aldoxorubicin is another attempt at improving on an old, active sarcoma drug. The developers of aldoxorubicin have attempted to exploit the phenomena of increased vascular permeability and altered interstitial fluid movement in cancer to enhance drug delivery to tumor. They have pursued this strategy by altering the drug to bind albumin, a macromolecule able to accumulate in cancer interstitial space. Aldoxorubicin is a thiol-binding prodrug of doxorubicin. On entry into the bloodstream, aldoxorubicin rapidly binds to the cysteine-34 position of circulating albumin via a pH-sensitive linker.1 Albumin is the largest source of free sulfhydryl in human serum, and the thiol group at cysteine-34 is highly reactive at neutral pH. Pharmacokinetic studies have demonstrated that most (~90%) aldoxorubicin binds covalently to albumin within minutes and only very low levels of doxorubicin and the metabolite, doxorubicinol, can be detected in plasma. In addition, the volume of distribution of aldoxorubicin is small, suggesting very little diffusion of drug into tissue or blood cells.2

In an acidic environment (such as in hypoxic regions of cancer), the hydrazine linker between doxorubicin and native albumin is hydrolyzed, resulting in release of active doxorubicin.3 In this issue of JAMA Oncology, Chawla and colleagues4 report the results of a prospective, randomized phase IIb trial in which patients with metastatic soft-tissue sarcoma were randomized in a 2:1 fashion to first-line treatment with aldoxorubicin at the established maximum tolerated dose of 350 mg/m² (equivalent to 260 mg/m² of doxorubicin)4 or doxorubicin 75 mg/m² administered every 3 weeks. Randomization was stratified by Eastern Cooperative Oncology Group performance status and whether prior adjuvant or neoadjuvant chemotherapy had been administered but not by tumor grade or region of treatment (eg, United States, Europe, Australia, Russia, India). The study design included careful cardiac evaluation and blinded, independent assessment of tumor response. Patients who received aldoxorubicin experienced a significantly longer median progression-free survival (5.6 vs 2.7 months;