Gemcitabine and Docetaxel in Metastatic Sarcoma: Past, Present, and Future

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ABSTRACT

Objective. In the era of oral molecular kinase inhibitors, cytotoxic chemotherapy agents are somewhat overlooked, but remain the backbone of treatment for most cancers. Patients with non-gastrointestinal stromal tumor sarcomas, such as leiomyosarcoma, liposarcoma, and undifferentiated high-grade pleomorphic sarcoma (formerly called malignant fibrous histiocytoma), have received doxorubicin and ifosfamide as the backbone of their treatment for over 15 years or more. The goal of this article is to review the data that have led to the use of gemcitabine and docetaxel as a useful combination for patients with metastatic sarcomas, and to comment on possible synergy of the combination.

Methods and results. The literature regarding the use of gemcitabine, docetaxel, or both, is reviewed, with emphasis on patients with metastatic sarcomas.

Results. Activity of gemcitabine and docetaxel is observed in leiomyosarcoma and undifferentiated high-grade pleomorphic sarcoma. There is apparent schedule dependence of the combination in other cancers; it is unclear if schedule matters in patients with sarcomas. The dose and schedule of gemcitabine and docetaxel examined in phase II studies are probably too high for routine practice.

Conclusions. The combination of gemcitabine and docetaxel is an effective option for patients with metastatic sarcoma, increasing the armamentarium for the practicing oncologist in treating this heterogeneous group of diseases. Given the low response rate to docetaxel as a single agent, it is likely that there is true clinical synergy of the combination. The Oncologist 2007;12:999–1006

INTRODUCTION

Sarcomas are a heterogeneous group of cancers of soft tissue and bone, affecting approximately 13,000 people a year in the U.S. in 2007 [1]. Beyond diagnoses of gastrointestinal stromal tumor (GIST), leiomyosarcoma, liposarcoma, and undifferentiated high-grade pleomorphic sarcoma (UPS, formerly termed malignant fibrous histiocytoma [MFH]), there are at least 50 other soft tissue sarcoma variants that oncologists must address. Some of these are extremely rare, affecting no more than 25–50 people in the U.S. annually. This does not mean the field is impenetrable. In fact, if one has a good understanding of the behavior of the sarcomas mentioned above and the most common bone sarcomas (osteogenic sarcoma, Ewing’s sarcoma, and chondrosarcoma), it is possible to manage a distinct majority of cases encountered in clinical practice.

The data regarding imatinib and sunitinib in GISTs have shown medical oncologists the efficacy of kinase-specific
therapy for specific sarcoma subtypes. It is increasingly appreciated that each sarcoma subtype must be treated differently, much as one manages each of the hematological malignancies as a separate entity, and even more to the point, as a unique entity driven by specific genetic events. Sarcomas are akin to hematological malignancies in that as many as one third are associated with reproducible genetic changes (mutations or subtype-specific chromosomal translocations) that highlight the need to treat each entity as a specific type of cancer. Interestingly, some of these chromosomal alterations render the tumor relatively sensitive to chemotherapy (e.g., Ewing’s sarcoma, synovial sarcoma) while other translocations are associated with near complete resistance to standard cytotoxic chemotherapy (e.g., GIST, extraskeletal myxoid chondrosarcoma, alveolar soft part sarcoma).

Doxorubicin and ifosfamide, either alone or in combination, have served as the backbone for metastatic sarcoma therapy for over 15 years. With the limited number of drugs available for sarcoma, there has been an ongoing search for new agents for specific sarcoma subtypes, be they cytotoxic or cytostatic. Two useful pairings of other chemotherapeutic agents and sarcoma subtypes found over the last 15 years of testing include taxanes in angiosarcoma [2] and the novel chemotherapeutic agent trabectedin (not approved for commercial use as of mid-2007) in myxoid-round cell liposarcoma [3] and probably in other histologies [4–6]. The chemotherapeutic combination of gemcitabine and docetaxel has been shown to be an effective combination of cytotoxic agents against sarcomas in at least three phase II studies and one randomized study. In this article, we review the data regarding each drug’s pharmacology as a rationale for use of the combination. The studies are reviewed in the context of identifying sarcoma subtypes most sensitive to the combination. A few words in closing highlight future potential directions for this combination.

**DOCE TAXEL AND SARCOMAS**

Docetaxel is an agent that stabilizes tubulin, inhibiting the dynamic reorganization of the microtubular network of the cell, resulting in inhibition of mitotic and interphase cellular functions [7, 8]. Besides affecting microtubules (and mitosis in particular), taxanes also appear to have other functions in the tumor cell to disrupt cell growth [9]. Expression of multidrug resistance genes and mutations in beta-tubulin appear to be two important mechanisms of resistance to taxanes. Docetaxel is typically given as a 1-hour infusion once every 3 weeks, and with this schedule has linear pharmacokinetics up to ~115 mg/m² [10]. Its elimination best follows a three-compartment model. In a pooled analysis, it had a terminal half-life of 10.4 hours, clearance of 35 l/hour-m², and apparent distribution volume (Vd) at steady state of 67.3 l/m². Both the Vd and clearance are high, indicating extensive drug distribution and/or protein binding [11].

Docetaxel as a single agent (100 mg/m² i.v. every 3 weeks) was examined as second-line therapy in a phase II study from the European Organization for Research and Treatment of Cancer [12]. While it was found to have a 17% partial response (PR) rate in second-line therapy (5 of 29 patients), a follow-up randomized, phase II study examining doxorubicin versus docetaxel as first-line therapy, crossing over to the other therapy as second-line therapy, showed a 0% response rate (83 evaluable patients) for docetaxel in first- and second-line therapy [13]. Thus, the activity of docetaxel appears quite limited. It should be noted that angiosarcomas are one type of sarcoma sensitive to taxanes, with most of the literature referring to paclitaxel [2]; docetaxel has been reported to be active in case reports of patients with metastatic or locally advanced angiosarcoma [14].

**GEMCITABINE**

Gemcitabine (2’,2’-difluorodeoxycytidine, also abbreviated dFdC) also has a mechanism of action different from that of doxorubicin, ifosfamide, and dacarbazine. Gemcitabine is a fluorinated analogue of the nucleoside deoxyctydine (dCTP). Though it is inactive in its parent form, successive intracellular phosphorylation of the parent drug yields active di- and triphosphate metabolites [15]. The diphosphate form inhibits ribonucleotide reductase; the triphosphate form is incorporated into DNA and competes with dCTP as a fraudulent base (dFdCTP). The inhibition of ribonucleotide reductase may allow for a self-potentiating mechanism to increase nucleotide incorporation in cells [16]. Once the gemcitabine triphosphate metabolite is incorporated into DNA, one additional nucleoside is incorporated, after which DNA chain synthesis is terminated. This “masked chain termination” leaves the fraudulent base resistant to excision repair by DNA repair enzymes, and may overcome an important mechanism of drug resistance [17].

In key studies performed at the M.D. Anderson Cancer Center, the ability of cells to accumulate gemcitabine triphosphate was found to be saturable at gemcitabine dose rates that produce plasma gemcitabine levels of 10–25 µM [18]. The recommended phase II dosing for solid tumors was 790 mg/m² per week, weekly for 3 weeks, every 28 days. To render gemcitabine more effective, that study suggested that a longer exposure to drug may be associated with a greater antitumor effect, by maximizing the amount of gemcitabine that can accumulate intracellularly in a given time period.
The proposition that prolonged-infusion gemcitabine (10 mg/m² per minute) results in higher clinical response rates than with bolus infusions was addressed in a randomized phase II trial in pancreatic cancer [19]. Patients were all treated on days 1, 8, and 15, every 28 days. Response rates and median survival were superior for the 43 patients who received gemcitabine in a fixed-dose-rate infusion (1,500 mg/m² at 10 mg/m² per minute), compared with the 49 patients who received gemcitabine as a 30-minute bolus infusion (2,200 mg/m² i.v. over 30 minutes); the median survival times were 8 months and 5 months, respectively, \( p = .013 \). Of note, despite the lower dose and lower concentration of gemcitabine triphosphate at 30 minutes, the median maximum concentration for gemcitabine triphosphate in peripheral blood mononuclear cells was greater than that for the bolus infusion (398 versus 188 \( \mu M \); \( n = 16 \) patients assayed; \( p = .046 \) for the 150-minute time point) [19]. Thus, it was logical to examine a fixed-dose rate of gemcitabine in patients with sarcomas. The pharmacodynamics of gemcitabine in patients with sarcoma were consistent with those found in the pancreatic cancer study [20].

GEMCITABINE AND DOCETAXEL: POSSIBLE SYNERGY?

Several investigators have probed whether gemcitabine and docetaxel may be synergistic in vitro. Many of these studies are summarized in a thorough review of gemcitabine combinations with antimetabolites in preclinical and clinical studies [32]. Gemcitabine and docetaxel applied simultaneously to lung cancer cell lines were antagonistic with one another, and were somewhat less than additive when gemcitabine preceded paclitaxel or vice versa [33]. Zoli et al. [34] showed that gemcitabine given before docetaxel was modestly synergistic in non-small cell lung cancer cell lines. Docetaxel given before gemcitabine (with a washout period) engendered significant synergy, perhaps from synchronizing the cell line to the effects of gemcitabine.

These in vitro data suggested the synergy of the sequence docetaxel \( \rightarrow \) gemcitabine (D\( \rightarrow \)G) over gemcitabine \( \rightarrow \) docetaxel (G\( \rightarrow \)D) in lung cancer cell lines (and thus in patients). However, different data were observed comparing D\( \rightarrow \)G with G\( \rightarrow \)D (24-hour exposure each) in the MCF-7 breast carcinoma cell line versus the SaOS-2 osteogenic sarcoma cell line [35]. Whereas simultaneous exposure to both drugs was additive in SaOS-2 cells, the combination was antagonistic in the MCF-7 cell line. Furthermore, while both D\( \rightarrow \)G and G\( \rightarrow \)D were synergistic in MCF-7 cells, only G\( \rightarrow \)D was synergistic in SaOS-2 cells, while D\( \rightarrow \)G was antagonistic. These data imply that different cancers may have different sensitivities to the gemcitabine and docetaxel schedule, and hint at a possible difference in response between mesenchymal and epithelial neoplasms to this combination.

Unfortunately, the importance of sequence of gemcitabine and docetaxel has been addressed directly in only one phase I study [36]. As part of this examination of gemcitabine and docetaxel, pharmacokinetics for the D\( \rightarrow \)G and G\( \rightarrow \)D sequences were examined. The mean gemcitabine concentrations 30 and 90 minutes after starting a gemcitabine infusion were significantly lower after docetaxel pretreatment, but the elimination half-life was longer after such exposure, suggesting a change in drug partitioning among different blood constituents (cells, plasma proteins, plasma water) [36]. Another variable not examined in the phase I study was the fixed-dose-rate infusion schedule of gemcitabine with docetaxel.

As noted below in the section on clinical studies, gemcitabine pharmacokinetics were also examined in a phase II study of gemcitabine and docetaxel. In that study, gemcitabine was given on day 1 of successive cycles of therapy over 30 or 90 minutes, a day on which docetaxel was not administered. Not surprisingly, peak levels of gemcitabine were lower in infusing the same amount of gemcitabine over 90 minute versus 30 minutes. However, notably, the time above a threshold of 10 \( \mu M \) was greater with the longer infusion time of gemcitabine (1.3 versus 0.88 hours; \( p = .0008 \)) [37]. These data support the concept of the benefit of the fixed-dose-rate infusion highlighted in the pharmacodynamic studies of nucleotide accumulation noted above.

Thus, several levels of heterogeneity are highlighted in the studies of gemcitabine and docetaxel to date: (a) effects on the effective gemcitabine concentration and intracellular gemcitabine triphosphate accumulation depend on the duration of drug infusion, (b) there are differences in the dis-
<table>
<thead>
<tr>
<th>Study</th>
<th>Gemcitabine dose and schedule</th>
<th>Clinical trial design</th>
<th>n (evaluable)</th>
<th>Prior therapy</th>
<th>Responses and response rate</th>
<th>Response definition</th>
<th>Median TTP (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amodio et al. [22]</td>
<td>1,000–1,250 mg/m² over 30 minutes, 3 wks on, 1 off</td>
<td>Phase II</td>
<td>18</td>
<td>Any</td>
<td>1 PR (6%, MFH)</td>
<td>n/a</td>
<td>4</td>
<td>n/a</td>
</tr>
<tr>
<td>Merimsky et al. [23]</td>
<td>1,000 mg/m² over 30 minutes weekly \times 7, 1-wk break, then 3 wks on, 1 off</td>
<td>Phase II</td>
<td>18</td>
<td>Yes</td>
<td>1 PR (6%, uterine LMS)</td>
<td>WHO</td>
<td>6.2</td>
<td>n/a</td>
</tr>
<tr>
<td>Spath-Schwalbe et al. [24]</td>
<td>200–250 mg/m² over 360 minutes, 3 wks on, 1 off</td>
<td>Phase II</td>
<td>18</td>
<td>Yes</td>
<td>2 PRs (11%, 2 uterine LMS)</td>
<td>WHO</td>
<td>n/a</td>
<td>8</td>
</tr>
<tr>
<td>Patel et al. [20]</td>
<td>Standard schedule; some received 1 g/m² over 150 minutes</td>
<td>Phase II</td>
<td>39 (non-GIST)</td>
<td>Any</td>
<td>7 PRs (18%, 4 LMS [3 uterine], 1 MFH, 1 sarcoma NOS, 1 angiosarcoma)</td>
<td>WHO</td>
<td>3.0</td>
<td>13.9</td>
</tr>
<tr>
<td>Okuno et al. [25]</td>
<td>1,250 mg/m² over 30 minutes, 3 wks on, 1 off</td>
<td>Phase II</td>
<td>29</td>
<td>First-line</td>
<td>1 PR (3%, uterine LMS)</td>
<td>WHO</td>
<td>6-month TTP, est. 11%</td>
<td>1-yr est. overall survival, 43%</td>
</tr>
<tr>
<td>Švancárová et al. [26]</td>
<td>1,250 mg/m² over 30 minutes, 2 wks on, 1 off</td>
<td>Phase II</td>
<td>32</td>
<td>First-line</td>
<td>1 PR (3%, LMS)</td>
<td>WHO</td>
<td>1.5</td>
<td>8.8</td>
</tr>
<tr>
<td>Okuno et al. [27]</td>
<td>1,250 mg/m² over 30 minutes, 3 wks on, 1 off</td>
<td>Phase II</td>
<td>25</td>
<td>None</td>
<td>1 PR (4%, epithelioid sarcoma)</td>
<td>WHO</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Look et al. [28]</td>
<td>1,000 mg/m² over 30 minutes, 3 wks on, 1 off</td>
<td>Phase II</td>
<td>42 (all uterine LMS)</td>
<td>First-line</td>
<td>1 CR, 8 PRs (21%, all uterine LMS)</td>
<td>GOG</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Hartmann et al. [29]</td>
<td>1,000 mg/m² over 30 minutes, 3 wks on, 1 off</td>
<td>Phase II</td>
<td>15</td>
<td>First-line</td>
<td>1 PR (6%, n/a)</td>
<td>WHO</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Von Burton et al. [30]</td>
<td>Standard schedule</td>
<td>Phase II</td>
<td>36</td>
<td>None</td>
<td>3 PRs (8%, 1 MFH, 1 LMS, 1 sarcoma NOS)</td>
<td>SWOG</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Wagner-Bohne et al. [31]</td>
<td>1,200 mg/m² over 30 minutes, 3 wks on, 1 off</td>
<td>Phase II</td>
<td>20 (pediatric diagnoses)</td>
<td>Any</td>
<td>0</td>
<td>RECIST</td>
<td>1.5</td>
<td>n/a</td>
</tr>
<tr>
<td>Maki et al. [41]</td>
<td>1,200 mg/m² over 120 minutes</td>
<td>Randomized phase II (one arm)</td>
<td>49</td>
<td>0–2</td>
<td>4 (9%, 1 LMS, 2 MFH, 1 other)</td>
<td>RECIST</td>
<td>3.0</td>
<td>11.5</td>
</tr>
</tbody>
</table>

*Indicated as “standard schedule” in remainder of the table.

Abbreviations: CR, complete response; est., estimated; GIST, gastrointestinal stromal tumor; GOG, Gynecological Oncology Group; LMS, leiomyosarcoma; MFH, malignant fibrous histiocytoma (undifferentiated high-grade pleomorphic sarcoma); n/a, not available; NOS, not otherwise specified; OS, overall survival; PR, partial response; RECIST, Response Evaluation Criteria for Solid Tumors; SWOG, Southwest Oncology Group; TTP, time to progression; WHO, World Health Organization.
tribution and clearance of gemcitabine in the presence or absence of docetaxel, and (c) there is a potential schedule dependence against a given type of cancer (e.g., epithelial versus mesenchymal), and perhaps even within a specific type of cancer. At present, there remain only hints of preclinical data that support the idea that gemcitabine and docetaxel are synergistic in the treatment of sarcomas or other cancers.

**GEMCITABINE AND DOCETAXEL: CLINICAL STUDIES (TABLE 2)**

Given what was perhaps more promising data from other clinical trials rather than preclinical data, Hensley et al. [37] examined gemcitabine and docetaxel in a phase II study of patients with metastatic leiomyosarcoma. That study also examined the pharmacokinetics of gemcitabine in a 30- and 90-minute infusion schedule on separate cycles of therapy, described above. The study enrolled 34 patients, all but five with uterine leiomyosarcoma, and demonstrated a surprising response rate of 53% (three complete responses, 15 PRs). Importantly, 50% of patients previously treated with doxorubicin responded. The median time to progression was 5.6 months, and the median survival duration was 17.9 months [37]. This study was impressive in its demonstration of uterine leiomyosarcoma as a subtype relatively sensitive to this chemotherapy combination, and also indicated that part of the reason for this high response rate was the synergy of gemcitabine and docetaxel, given the 21% response rate for gemcitabine alone in second-line therapy in a Gynecologic Oncology Group (GOG) study [28] and low response rate of docetaxel against sarcomas in first- and second-line therapy in phase II and randomized phase II studies [13].

These data were supported by two other clinical studies of patients consecutively treated with gemcitabine and docetaxel at the University of Michigan [35] and in a retrospective analysis of patients treated with gemcitabine plus docetaxel in France [38]. In the clinical analysis from Michigan, the response rate for patients treated mostly with first- and second-line therapy was 43%; the response rate in the French cohort of patients receiving any number of lines of prior therapy was 18% [38]. These data confirmed the ac-

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose and schedule</th>
<th>Trial design</th>
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<th>Prior therapy</th>
<th>Responses and response rate</th>
<th>Response definition</th>
<th>Median TTP (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hensley et al. [37]</td>
<td>G, 900 mg/m² over 90 minutes days 1 and 8; D, 100 mg/m² day 8</td>
<td>Phase II</td>
<td>34 (LMS, 29 uterine)</td>
<td>0–2</td>
<td>3 CRs, 15 PRs (53%, all LMS)</td>
<td>RECIST</td>
<td>5.6</td>
<td>17.9</td>
</tr>
<tr>
<td>Leu et al. [35]</td>
<td>G, 675 mg/m² over 60 minutes days 1 and 8; D, 100 mg/m² day 8</td>
<td>Retrospective</td>
<td>35</td>
<td>Any</td>
<td>5 CRs, 10 PRs (43%, 7 LMS, 1 MFH, 2 osteosarcoma, 3 angiosarcoma, 1 MPNST, 1 Ewing’s sarcoma)</td>
<td>RECIST</td>
<td>6.7</td>
<td>13</td>
</tr>
<tr>
<td>Bay et al. [38]</td>
<td>G, 900 mg/m² over 90 minutes days 1 and 8; D, 100 mg/m² day 8</td>
<td>Retrospective</td>
<td>114</td>
<td>Any</td>
<td>3 CRs, 18 PRs (18%; 16 LMS, 5 other)</td>
<td>WHO</td>
<td>n/a</td>
<td>12.1</td>
</tr>
<tr>
<td>Maki et al. [41]</td>
<td>G, 900 mg/m² over 90 minutes days 1 and 8; D, 100 mg/m² day 8</td>
<td>Randomized phase II (one arm)</td>
<td>73</td>
<td>0–2</td>
<td>2 CRs, 10 PRs (16%, 5 LMS, 4 MFH, 2 Pleomorphic liposarcoma, 1 RMS)</td>
<td>RECIST</td>
<td>6.2</td>
<td>17.9</td>
</tr>
</tbody>
</table>

*Abbreviations: CR, complete response; D, docetaxel; G, gemcitabine; LMS, leiomyosarcoma; MFH, malignant fibrous histiocytoma (undifferentiated high-grade pleomorphic sarcoma); MPNST, malignant peripheral nerve sheath tumor; n/a, not available; OS, overall survival; PR, partial response; RECIST, Response Evaluation Criteria for Solid Tumors; RMS, rhabdomyosarcoma; TTP, time to progression; WHO, World Health Organization.*

*Doses reduced for prior pelvic radiation.*
tivity of gemcitabine and docetaxel in leiomyosarcoma, with patients with a few other histologies responding as well.

The question remained whether the activity of gemcitabine and docetaxel lay in the fixed-dose-rate infusion schedule (10 mg/m^2 per minute) or in the synergy between gemcitabine and docetaxel. The Sarcoma Alliance for Research through Collaboration (SARC) performed a randomized phase II study to examine this question, comparing between patients given a higher dose fixed-dose-rate infusion of gemcitabine and those given a lower dose of fixed-dose-rate gemcitabine and docetaxel. A novel Bayesian clinical trial design was employed that randomized patients to the better therapy as the study proceeded. The details of the model and the interpretation of the study design are described elsewhere [39, 40]. In all, 73 patients were randomized to the two-drug combination, and 49 were randomized to gemcitabine as a single agent, indicating in and of itself the superiority of the combination [41]. The response rate for gemcitabine was 9%, versus 16% for gemcitabine and docetaxel, and more patients on the combination took longer to progress than on the single agent, accounting for the model’s imbalance of randomization in favor of the combination.

Interestingly, the response rate for patients with leiomyosarcoma was 11% for gemcitabine alone (1 in 9 patients) and 17% (5 in 29 patients) for the combination, while the response rate for UPS (MFH) was 25% (2 of 8 patients) with gemcitabine and 36% (4 of 11 patients) with the combination, indicating that UPS/MFH, like leiomyosarcoma, is sensitive to both gemcitabine and the gemcitabine plus docetaxel combination, perhaps to an even greater degree than leiomyosarcoma. These data confirm the use of gemcitabine and docetaxel as an effective salvage therapy for doxorubicin- and/or ifosfamide-refractory patients [41].

It is important to recognize that gemcitabine and docetaxel is potentially associated with significant toxicity. Pulmonary toxicity and refractory peripheral edema are the most common severe adverse events worth noting [42, 43]. Thrombocytopenia and neutropenia are common, even with the use of growth factor support [41]. However, the febrile neutropenic rate was low. Nonetheless, what were largely constitutional effects of gemcitabine and docetaxel led to its discontinuation in as many as 50% of the patients who stayed on therapy for 6 months or more, indicating that the doses used in the clinical trial were too high for routine use. The author notes that activity of the combination has been observed anecdotally in patients using a schedule with lower doses of docetaxel, but these decisions have to be made on a patient-by-patient basis.

### Future Directions for Gemcitabine and Docetaxel

Despite numerous clinical trials of the combination of gemcitabine and docetaxel, there remains a remarkable amount of data missing regarding the pharmacokinetics and pharmacodynamics of the combination. Given the clinical response rates to gemcitabine and docetaxel alone in comparison with the combination, it appears there is some degree of synergy between gemcitabine and docetaxel, though a purely additive effect of the two agents cannot be ruled out. The clinical synergy of gemcitabine and docetaxel differs from the case of doxorubicin and ifosfamide, in which there does not appear to be synergy but probably only additivity (at best) of the two agents’ activity in patients with sarcoma [44].

Several questions remain regarding gemcitabine and docetaxel, some of which are being addressed presently in their own clinical trials.

1. Are gemcitabine and docetaxel useful in the adjuvant setting? This question is being examined in a phase II study from SARC of gemcitabine and docetaxel followed by cycles of single-agent doxorubicin in patients with primary uterine leiomyosarcomas, the most sensitive site and subtype of sarcomas observed to date. If significant time to recurrence is observed with this combination of agents, a formal phase III study would be able to confirm or refute the combination’s activity.

2. Is the combination useful in other uterine histologies? A phase II study of gemcitabine and docetaxel is being offered by the GOG for patients with carcinosarcoma of the uterus (also called malignant mixed Müllerian tumor of the uterus) using gemcitabine on a 30-minute infusion schedule. The French Sarcoma Group is examining gemcitabine versus gemcitabine and docetaxel in its own phase II randomized study in patients with uterine (and other) leiomyosarcomas. It is also unknown if the combination of gemcitabine and paclitaxel would have any different degree of efficacy than gemcitabine and docetaxel. Given the nature of drug development in the present day, the author speculates it is more likely that we would see an examination of gemcitabine and paclitaxel albumin-bound particles (the latter of which has higher response rates than paclitaxel alone in other cancers) long before we see a comparative trial involving gemcitabine and paclitaxel.

3. Can the effectiveness of gemcitabine plus docetaxel be enhanced by growth factor or kinase-specific therapeutics? The GOG is examining the combination of gemcitabine and docetaxel and bevacizumab in a phase II study. The utility of other small-molecule inhibitors of the vascular endothelial growth factor pathway, such as sunitinib or sorafenib, with this combination, or with combinations
involving other kinase pathway–specific agents, is not clear. It will be particularly helpful to have in vitro data to indicate which of these agents might be beneficial to combine with gemcitabine and docetaxel in vitro or in xenograft studies before moving forward with a clinical study.

4. Are gemcitabine and docetaxel active enough to be considered first-line therapy for metastatic sarcomas? Doxorubicin and ifosfamide is associated with a significant response rate in soft tissue sarcomas, but response rates and survival data may differ from one study to the next based on both patient histologies included in a specific clinical trial and the era in which the study was performed. The medical oncology group at the University of Michigan is examining the question of the best first-line therapy for sarcomas, comparing the standard doxorubicin and ifosfamide combination with the gemcitabine and docetaxel combination in first-line therapy for patients presenting with metastatic sarcomas.

Other questions that remain unanswered by a clinical trial open at present include:

Is there any difference in response or time to progression in patients treated with G→D versus D→G?

How do the pharmacokinetics and pharmacodynamics of gemcitabine change with the fixed dose rate infusion in the presence of taxanes?

Can one give lower doses of docetaxel and still see synergy of the combination? Parenthetically, by doubling the number of beta-tubulin adducts created with docetaxel administration, one nearly certainly does not double the response rate. Conversely, is there any benefit to increasing the dose of gemcitabine or docetaxel in a future study? Based on the data with gemcitabine alone (Table 1), this would appear to not be the case.

Is there any benefit to altering the gemcitabine and docetaxel schedule to improve efficacy?

Are there other subtypes of sarcomas that may be particularly responsive to this combination, but have been only infrequently tested because of their extremely low incidence?

Good research often raises more questions than it answers. It is clear that preclinical and clinical studies appreciating pharmacokinetic and pharmacodynamic parameters of this combination are still lacking. Such preclinical and pharmacokinetic/pharmacodynamic research, as well as the clinical trials noted above being performed at present or in the near future, will hopefully provide a greater understanding of this antimitabolite–taxane combination and its place in the treatment of sarcomas and other cancers.

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DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST
The author indicates no potential conflicts of interest.


