



Evidence-Based Series 11-11 ARCHIVED 2017

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

**Chemotherapy (i.e., Gemcitabine, Docetaxel Plus Gemcitabine,
Doxorubicin, or Trabectedin) for Inoperable, Locally Advanced,
Recurrent, or Metastatic Uterine Leiomyosarcoma**

*A. Gupta, X. Yao, S. Verma, H. Mackay, L. Hopkins,
the Sarcoma Disease Site Group (DSG), and the Gynecology Cancer DSG*

Report Date: July 18, 2012

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Section 1: Guideline Recommendations
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process

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Evidence-Based Series 11-11: Section 1

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Chemotherapy (i.e., Gemcitabine, Docetaxel Plus Gemcitabine, Doxorubicin, or Trabectedin) for Inoperable, Locally Advanced, Recurrent, or Metastatic Uterine Leiomyosarcoma: Guideline Recommendations

*A. Gupta, X. Yao, S. Verma, H. Mackay, L. Hopkins,
the Sarcoma Disease Site Group (DSG), and the Gynecology Cancer DSG*

Report Date: July 18, 2012

QUESTIONS

1. Does chemotherapy (i.e., gemcitabine, gemcitabine plus docetaxel, doxorubicin, or trabectedin) improve clinical outcomes (i.e., tumour response rate, progression-free survival [PFS], overall survival [OS], toxicity, or quality of life [QOL]) in women with inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma (LMS)?
2. Is there a difference in tumour response rate to chemotherapy (i.e., gemcitabine, gemcitabine plus docetaxel, doxorubicin, or trabectedin) between recurrent pelvic disease compared with extra-pelvic metastases in patients with uterine LMS?

TARGET POPULATION

Women with inoperable, locally advanced, recurrent, or metastatic uterine LMS.

INTENDED USERS

Medical oncologists, gynecologic oncologists, general surgeons, radiation oncologists, pharmacists, and other clinicians who take care of the above target patients.

RECOMMENDATIONS AND KEY EVIDENCE

In the absence of randomized controlled trials (RCTs) comparing chemotherapy with no treatment controls for inoperable, recurrent, or metastatic LMS of the uterus, the Sarcoma DSG and Gynecologic Cancer DSG offer the following recommendations:

- Doxorubicin alone or gemcitabine alone or gemcitabine plus docetaxel may be treatment options as first and/or second line therapy for women with inoperable, locally advanced, recurrent, or metastatic uterine LMS, based on current available evidence from the medical literature (four single-arm phase II studies, one arm of an RCT, and one abstract).
 - Hematological toxicity is common and should be monitored, and granulocyte growth factor (G-CSF) should be considered when gemcitabine plus docetaxel is used.
 - Other toxicities, such as neurotoxicity, pulmonary or cardiovascular toxicity, should be monitored.
- No recommendation is made for or against using trabectedin in the targeted patients.

- Patients should be encouraged to participate in clinical trials testing novel or targeted approaches in this disease.

Qualifying Statement

- The following chemotherapy agent doses were suggested from the included studies:
 - Doxorubicin: 60-80 mg/m² intravenously (IV) every 3 weeks;
 - Gemcitabine: 1000 mg/m² IV on days 1, 8, and 15 every 4 weeks;
 - Gemcitabine plus docetaxel: gemcitabine 900 mg/m² IV on days 1 and 8, followed by docetaxel 100 mg/m² IV on day 8 every 3 weeks.

Key Evidence

- There are no trials of high methodological quality that document the outcomes of patients with advanced or metastatic uterine LMS when no systemic therapy is employed. Doxorubicin has been considered a ‘standard of care’ for over 30 years.
- Survival and response rate and toxicity for each regimen are shown below:

| Chemotherapy | 1 st /2 nd line therapy | Median OS | Median PFS | Response rate (CR+PR) | Grades 3-4 toxicity | |
|--------------------------------|---|----------------------------------|------------|--------------------------------------|---|----|
| Doxorubicin ^a (1) | 1 st /2 nd | 12.1 mo | NR | 25% (95% CI, 9-41%) | Leucopenia: 16%, thrombocytopenia: 4%; Questionable cardiac toxicity: 3% (no detail) | |
| Gem ^b (2) | 2 nd | NR | NR | 21% (CI, 7-31%) | Leucopenia: 27%, thrombocytopenia: 11%, RBC transfusion: 9%; Neurotoxicity: 5%; Pulmonary toxicity: 5%; Cardiovascular toxicity: 5% (no detail) | |
| Gem+Doc ^c (3-5) | 1 st /2 nd | 14.7-16.1 mo | 4.4-6.7 mo | 27% (CI, 15-42%) to 53% (CI, 35-70%) | Leucopenia: 14-23%, thrombocytopenia: 14-40%, RBC transfusion: 43-50%; Neurotoxicity: 0-6%; Pulmonary toxicity: 0-8% | |
| Gem vs. Gem+Doc (abstract) (6) | Gem | 1 st /2 nd | NR | 4.9 mo | 18% (CI, 2-34%) | NR |
| | Gem+Doc | 1 st /2 nd | NR | 6.0 mo | 23% (CI, 8-38%) | NR |

Abbreviations: OS = overall survival, PFS = progression-free survival, CR = complete response, PR = partial response, CI = confidence interval, NR = not reported, mo = months, Gem = gemcitabine, RBC = red blood cell, Doc = docetaxel, vs. = versus.

^a Adverse effects were assessed by their own criteria.

^b Standard Gynaecologic Oncology Group response criteria were used for toxicity grading.

^c The National Cancer Institute Common Toxicity criteria were used for toxicity grading.

- To date, there is insufficient evidence to support or refute the use of trabectedin in the targeted patients.
- There was no data on differences in response between recurrent pelvic disease and extra-pelvic metastases, or on QOL.

Justification for Recommendation

Doxorubicin alone has long been considered a standard treatment for patients with inoperable, locally advanced, recurrent, or metastatic soft tissue sarcoma (STS), including women with uterine leiomyosarcoma (7, 8).

The studies included in this systematic review must have reported at least one relevant outcome on 20 or more targeted patients. Studies that did not perform subset analyses for uterine LMS were excluded.

Although the Omura et al 1983 study used a dose of 60 mg/m² IV every 3 weeks for doxorubicin, this study was conducted almost 30 years ago, and a dose of 70-80 mg/ m² IV every 3 weeks has usually been used for locally advanced or metastatic STS since 1990 (9). Thus, the suggested dose for doxorubicin is 60 to 80 mg/m² IV every 3 weeks in the Qualifying Statement.

From single-arm studies, the studies of gemcitabine plus docetaxel have reported numerically longer median OS (14.7-17.9 months versus 12.1 months) and numerically higher objective response rates (27-53% versus 25%) than that reported in the study of doxorubicin alone. The combination of gemcitabine plus docetaxel resulted in more toxicity than did doxorubicin alone. As there has been no randomized comparison of these two regimens, no conclusions can be made regarding the superiority of gemcitabine plus docetaxel compared with doxorubicin. It is unlikely that such a comparative study will be undertaken; therefore, recommendations regarding gemcitabine plus docetaxel will be derived from phase II trial data. The only available study for single-agent gemcitabine reported a tumour response rate of 21%, which is not superior to the 25% response rate with doxorubicin alone; this trial did not report the OS or PFS information. Thus, it is unclear from this study whether gemcitabine alone can improve survival or PFS for the target patient. The only randomized data available is from an abstract (pooled data from two RCTs) (6) and failed to demonstrate the superiority of gemcitabine plus docetaxel over gemcitabine alone for tumour response rate and PFS or provide information about OS. However, the recommendations cannot be made based on published abstracts. Without published RCTs or good-quality comparative studies, and after considering the balance between the benefits and harms from these chemotherapeutic agents, one treatment option cannot be recommended over another (see additional discussion in Section 3). Hematological toxicity is common for all the treatment options. the use of G-CSF should be considered when gemcitabine plus docetaxel is used if the patient had private drug insurance to cover the cost of this drug. However, in the absence of private insurance, clinicians may consider dose reduction of chemotherapy and/or the addition of prophylactic oral antibiotics.

FUTURE RESEARCH

After searching the National Cancer Institute (NCI) clinical trials database (<http://www.cancer.gov/clinicaltrials>) on August 19, 2011 for ongoing trials, only one arm of an ongoing RCT, which investigated the effect of gemcitabine plus docetaxel, met the selection criteria for this systematic review. The other eight potentially included studies focus on patients with advanced STS and require confirmation of whether a subgroup analysis for 20 or more patients with advanced or recurrent uterine LMS will be included for each study. There are no eligible studies that address any differences in tumour response rate between pelvic and extra-pelvic metastases in patients with uterine LMS. Thus, there is a need for well-designed and good-quality RCTs to investigate the efficacy of chemotherapy in patients with inoperable, locally advanced, recurrent, or metastatic uterine LMS.

NOTE (November 9, 2012)

The Duffaud 2010 abstract (6) has been fully published in a peer-reviewed journal (10). Although there was no significant difference between gemcitabine alone and gemcitabine plus docetaxel in this paper (similar to the Duffaud 2010 abstract), this study is a phase II RCT lacking sufficient sample size calculation. It remains unclear whether the lack of difference seen is a result of the study being underpowered, or if there truly was no

difference. Thus, the working group members stand by our current recommendations. This guideline will follow CCO's PEBC's updating policy below.

Updating

This document will be reviewed in three years time to determine if it is still relevant to current practice and to ensure that the recommendations are based on the best available evidence. The outcome of the review will be posted on the CCO website. If new evidence that will result in changes to these recommendations becomes available before three years have elapsed, an update will be initiated as soon as possible.

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Evidentiary Base**

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QUESTIONS

1. Does chemotherapy (i.e., gemcitabine, gemcitabine plus docetaxel, doxorubicin, or trabectedin) improve clinical outcomes (i.e., tumour response rate, progression-free survival [PFS], overall survival [OS], toxicity, or quality of life [QOL]) in women with inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma (LMS)?
2. Is there a difference in tumour response rate to chemotherapy (i.e., gemcitabine, gemcitabine plus docetaxel, doxorubicin, or trabectedin) between recurrent pelvic disease compared with extra-pelvic metastases in patients with uterine LMS?

INTRODUCTION

Uterine sarcomas are a heterogeneous group of malignancies that include leiomyosarcoma (LMS), endometrial stromal sarcoma, adenosarcoma, and carcinosarcoma [1,2]. The pathology, staging [1], and clinical management of these four types are very different. The current review will focus on the role of systemic chemotherapy for uterine LMS exclusively.

In the United States, the incidence of uterine LMS is about 0.55 cases per 100,000 for white women and 0.92 cases per 100,000 for black women (3). In the absence of any systemic therapy, women diagnosed with unresectable advanced, recurrent, or metastatic disease will eventually succumb to their disease. Five-year disease-specific survival for women with high-grade FIGO (the International Federation of Gynecology and Obstetrics) stage IV disease is 27±6% (4). One CCO clinical guideline has recommended that single-agent doxorubicin remains the standard of care for women with advanced soft tissue sarcoma (STS), including those with uterine LMS (5). Single-agent doxorubicin is associated with a response rate of 16-27% and a median OS of 7.7-12 months (6). Gemcitabine and the combination of gemcitabine and docetaxel have recently been investigated as treatment alternatives to doxorubicin for patients with advanced STS and are now being used at many centres across North America (7). Trabectedin, a newer cytotoxic agent, has demonstrated activity in certain sarcoma subtypes (i.e., liposarcoma and synovial sarcoma) and was approved for the treatment of advanced STS by the European Medicines Agency in 2007 (8).

Is gemcitabine, gemcitabine plus docetaxel, or trabectedin more effective than doxorubicin in women with inoperable, locally advanced, recurrent, or metastatic uterine LMS

(Table 1)? Is gemcitabine plus docetaxel more effective than gemcitabine in uterine LMS? To clarify these questions, CCO's PEBC and the Sarcoma DSG and Gynecologic Cancer DSG (Appendix 1) decided to conduct a systematic review and develop a guideline on the appropriate treatment of women with inoperable, locally advanced, recurrent, or metastatic uterine LMS.

Table 1. Chemotherapy drugs considered for uterine leiomyosarcoma in this practice guideline and systematic review.

| Drug Name | Alternate Name |
|------------------|--|
| gemcitabine | Gemzar |
| docetaxel | Taxotere |
| doxorubicin | Adriamycin |
| trabectedin | ecteinascidin 743, ET-743, or yondelis |

METHODS

The evidence-based series (EBS) guidelines developed by the PEBC use the methods of the Practice Guidelines Development Cycle (9). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by the Working Group, which included three DSG members (Sarcoma DSG: SV, AG and Gynecology Cancer DSG: HM) and one methodologist from the PEBC (XY) (Appendix 1). All data were audited by a second, independent auditor. The available medical literature evidence forms the basis of the recommendations developed by the Sarcoma DSG and the Gynecology Cancer DSG, which are published in Section 1 of this document. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

In 2004, PEBC and the Gynecologic Cancer DSG developed a guideline on systemic therapy for advanced, recurrent, or metastatic uterine sarcoma by searching the literature from 1980 to June 2004 (10). This 2004 systematic review was used as the basis for this new updated review. Because the 2005 guideline included studies pertaining to all types of uterine sarcoma, only those that met the study selection criteria of this new guideline were eligible for inclusion in this review.

To update the 2004 systematic review, a literature search was performed using MEDLINE and EMBASE through the Ovid search engine from January 1, 2004, to June 17, 2011 to find eligible full texts. The search strategies are reported in Appendices 2 and 3. The following resources were checked for existing systematic reviews and practice guidelines, based on a systematic review: the Cochrane Library (to Issue 6, 2011), National Guideline Clearinghouse, National Health and Medical Research Council (Australia), New Zealand Guidelines Group, American Society of Clinical Oncology, National Comprehensive Cancer Network, National Institute for Health and Clinical Excellence, Scottish Intercollegiate guidelines Network, Society of Obstetricians and Gynaecologists of Canada, and Gynecologic Oncology Group (to June 16, 2011); and the Standards and Guidelines Evidence Inventory of Cancer Guidelines (11), which included over 1100 English-language cancer control guidelines and standards released from 2003 through June 2010 when it was checked on June 2, 2011.

The American Society of Clinical Oncology (ASCO) Annual Meeting Abstracts from 2005 to 2011 and Connective Tissue Oncology Society (CTOS) Annual Meeting Abstracts from 2005 to 2010 were checked for eligible abstracts.

Study Selection Criteria

Inclusion Criteria

Articles or abstracts were eligible for inclusion in this systematic review if they met all of the following criteria:

1. Full text reports were published from January 1, 2004, to June 17, 2011 or abstracts were published from January 1, 2005, to July 7, 2011.
2. Full text reports were systematic reviews, clinical practice guidelines based on a systematic review, randomized controlled trials (RCTs), or prospective studies; or published abstracts that were RCTs that investigated the effect of either gemcitabine, doxorubicin, or trabectedin alone, or in a combination of gemcitabine plus docetaxel.
3. Full text reports or abstracts reported at least one of the following clinical outcomes: tumour response rate, OS, toxicity, PFS, or QOL in women with inoperable, locally advanced, recurrent, or metastatic uterine LMS.
4. Studies reported at least one relevant outcome on 20 or more target patients.

Exclusion Criteria

Articles or abstracts were excluded if they met any of the following criteria:

1. Full text reports or abstracts were published in a language other than English.
2. They were non-systematic reviews, animal studies, letters, editorials, or commentaries.
3. Studies enrolled uterine LMS patients and other types of sarcoma patients but did not report any relevant outcome separately for uterine LMS patients.

Synthesizing the Evidence

If possible, a meta-analysis of each clinical outcome would be considered and conducted. Any data for which denominators were less than 30 should be considered carefully because they usually have an extremely large 95% confidence interval (CI) and are unlikely to be statistically significant.

STATA 11.0 would be the statistical software for statistical calculation purposes and for producing figures. A two-sided significance level of $\alpha = 0.05$ was assumed.

RESULTS

Literature Search Results

No clinical practice guidelines were found, based on the systematic review, that focused on the topic of chemotherapy in women patients with inoperable, locally advanced, recurrent, or metastatic uterine LMS.

Of 5048 citations identified from the MEDLINE and EMBASE searches (Figure 1), 4955 articles were excluded after reviewing the titles and abstracts, and 86 were disqualified after reviewing the full texts. Maki et al reported subgroup analyses for metastatic LMS patients with prior pelvic radiation (PPR) (n=13) and without PPR (n=25) in an RCT—the Sarcoma Alliance for Research through Collaboration (SARC002) study. Because only a portion of patients in the PPR group were uterine LMS, this article was excluded (12). Demetri et al investigated the effect of different doses of trabectedin in advanced or metastatic patients with liposarcoma or LMS in another RCT, but no subgroup outcome analysis was performed for uterine LMS patients; the corresponding author was contacted to clarify if they had other publications for uterine LMS patients, and no feedback was received; therefore, this article

was also excluded (13). One relevant systematic review of “clinical management of uterine sarcomas” was found (14), and all the included fully published studies in that review were retrieved by the MEDLINE and EMBASE searches in this systematic review, yielding three eligible articles (15-17). Two other eligible studies were found after checking the 2004 guideline (18,19). The reference lists of the included articles were hand-searched, and no further eligible papers were found.

A check of 2142 abstracts from the ASCO and CTOS Annual Meeting Abstracts yielded one abstract—Duffaud 2010 abstract that met the study selection criteria (20). This study pooled 12 uterine LMS patients from the SARCO02 study (no information for these 12 patients was in other publications included in this review) and 40 patients from a sub-RCT in the French TaxoGem study. The French TaxoGem study has not been published as a full text, but an abstract—Pautier 2009 abstract for the sub-RCT of uterine LMS patients was published in the ASCO 2009 Annual Meeting report (21). Unfortunately, this abstract did not report the relevant clinical outcomes, which were only shown in the oral presentation at that meeting (therefore, no paper publication records). The results from the oral presentation were unable to be cited, making the Pautier 2009 abstract ineligible for this systematic review. However, the data from this abstract was covered by the Duffaud 2010 abstract. Totally, five full texts and one abstract were included in this systematic review.

No studies found that addressed the second research question.

Study Design

Table 2 describes the study information and patient characteristics for the included studies. Of the five full-text publications, one is an RCT (18), and four are single-arm phase II studies (15-17, 19). In the RCT, only the arm that investigated the effect of doxorubicin in 41 patients met the inclusion criteria and was included; the other arm, which investigated the effect of doxorubicin plus dimethyl-triazeno-imidazole-carboxamide, did not meet the inclusion criteria, making it unsuitable for our research questions. The sample size for each study ranged from 34 to 51 individuals, with the total eligible sample size from the five full texts publication being 216. The patient age ranged from 29 to 84 years. Three single-arm trials with the same first author were independent studies and did not contain overlapping patients (This information was confirmed by the original corresponding author.) (16, 17, 19). In the eligible abstract (20), 52 patients with uterine LMS were extracted from two independent RCTs.

Figure 1. Flow of studies considered for this systematic review.

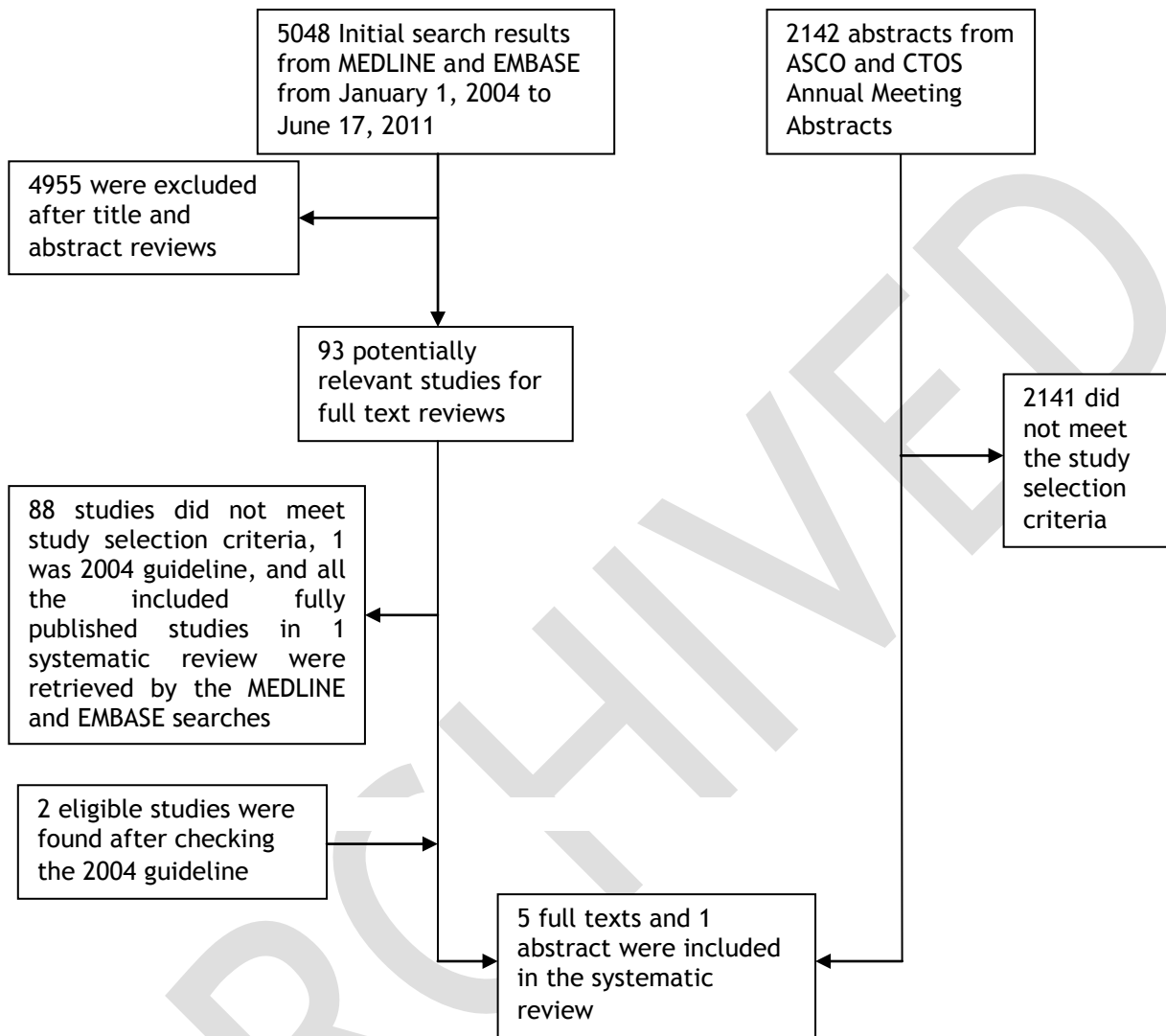


Table 2. Characteristics of included studies.

| Study | Country | Design | N; Age (median) | Tumour status at baseline |
|---------------------------------|--------------------------|---|-------------------------------|--|
| Omura 1983 (18) | United States | RCT, only one arm with doxorubicin therapy was eligible | 41; 29-84 (60) y ^a | Advanced |
| Hensley 2002 (19) | United States | Phase II | 34; 32-74 (54) y ^b | Inoperable |
| Look 2004 (15) | United States | Phase II | 48; 31-82 (53) y | Recurrent, persistent, or unresectable |
| Hensley 2008 (second-line) (16) | United States | Phase II | 51; 30-72 (50) y ^c | Advanced or recurrent |
| Hensley 2008 (first-line) (17) | United States | Phase II | 42; 33-73 (56) y | Advanced or recurrent |
| Duffaud 2010 [abstract] (20) | France and United States | A pooled analysis of two RCTs—the TG study and SAR002 study | 52; NR | Metastatic or relapsed |

Abbreviations: N = sample size of patients at the baseline, RCT = randomized controlled trial, y =years, TG Study = the French TaxoGem Study, SAR002 study = the Sarcoma Alliance for Research through Collaboration Study 002, NR = not reported.

^a This information was for 226 patients with various histological subtypes of uterine sarcoma.

^b The 34 patients included 29 uterine leiomyosarcoma (85%) and 5 other site leiomyosarcoma; 1 patient was male.

^c The age information was for 48 patients who were evaluated in this study.

Study Quality

The risk of bias of the Omura 1983 study (18) RCT was assessed with the modified Cochrane Collaboration tool (22) (Table 3a). There study provided no information about the randomization method, allocation concealment, blinding issue, follow-up time, planned sample size, or intention-to-treat analysis. The follow-up rate was 72%.

The four single-arm phase II studies (15-17,19) were assessed for study quality according to the modified Newcastle-Ottawa Scale (23) in Table 3b, which has been used in the Cochrane Collaboration non-randomized studies (NRS) method workshops to illustrate issues in data extraction from primary NRS (22). All the studies selected patients that could truly or somewhat represent the targeted patient population and had medical records for each patient, a proper follow-up rate and no bias of funding resources. However, blinding and follow-up time were unclear for all four studies, and only two demonstrated the outcome of interest at the start of the study.

Overall, the quality of evidence from the RCT was poor although only one arm was included in this systematic review, and the quality of evidence from the four phase II studies was moderate. No method detail was available for the Duffaud et al abstract to assess its quality.

Table 3a. Assessment of study quality for RCT by the modified Cochrane Collaboration Tool.

| Study | Randomization method | Allocation concealment | Blinding (participants, personnel, outcome assessment) | Follow-up time | Follow-up rate | Expected Effect, Power, and Planned Sample Size | Intention-to-treat analysis | Selective reporting | Funding |
|-----------------|----------------------|------------------------|--|----------------|----------------|---|-----------------------------|---------------------|--------------------------------------|
| Omura 1983 (18) | Unclear | Unclear | Unclear | NR | 72% | No | No | Unclear | The Gynecologic Oncology Group grant |

Abbreviations: RCT = randomized controlled trial, NR = not reported.

Table 3b. Assessment of study quality for prospective studies by the modified Newcastle-Ottawa Scale^a.

| Study | Selection | | | Outcome | | | Funding |
|---------------------------------|--|---------------------------|--|--|----------------|--------------------------------------|--|
| | Representativeness of the exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Blinded assessment of outcome ^b | Follow-up time | Adequate follow up rate ^c | |
| Hensley 2002 (19) | Yes ^d | Yes | Yes | Unclear | NR | Yes (100%) | National Institutes of Health/National Cancer Institute grant, American Cancer Society Clinical Research Training Grant, and Lili Research Laboratories Indianapolis |
| Look 2004 (15) | Yes | Yes | Yes | Unclear | NR | Yes (92%) | National Cancer Institute grants to the Gynecologic Oncology Group |
| Hensley 2008 (second-line) (16) | Yes | Yes | No | Unclear | NR | Yes (94%) | National Cancer Institute grants to the Gynecologic Oncology Group |
| Hensley 2008 (first-line) (17) | Yes | Yes | No | Unclear | NR | Yes (100%) | National Cancer Institute grants to the Gynecologic Oncology Group |

Abbreviations: NR = not reported.

^a The Newcastle-Ottawa Scale includes three domains: selection, comparability, and outcome; the domain of comparability, and one item (selection of the non-exposed group) under selection domain were not listed because no eligible study was a comparative trial. Funding column is added in this table. Yes = high quality; No = low quality.

^b The outcome assessors were blinded to the intervention/exposure.

^c Adequacy of follow-up was arbitrarily defined as $\geq 80\%$ of patients being analyzed for at least one of clinical outcomes.

^d The 34 patients included 29 with uterine LMS (85%) and 5 with other site LMS; 1 patient was male.

Outcomes

Meta-analyses of the trial results for tumour response rates on imaging, survival time, or toxicity were not feasible because of the differences in drug intervention, first- or second-line therapy, and tumour response and toxicity assessment measurement. No eligible study reported QOL.

Overall and Progression-Free Survival

Table 4 summarizes the outcome of survival. Four full texts and one abstract reported the median OS and/or PFS. The median OS for each regimen was as follows: doxorubicin as first- or second-line therapy, 12.1 months (18); gemcitabine plus docetaxel as first-line, 16.1 months (17); gemcitabine plus docetaxel as second-line, 14.7 months (16); and gemcitabine plus docetaxel as first- or second-line, 17.9 months (19). OS for gemcitabine alone was not available (15).

The median PFS for each regimen was as follows: doxorubicin as first- or second-line therapy, not available (18); gemcitabine plus docetaxel as first-line, 4.4 months (17); gemcitabine plus docetaxel as second-line, 6.7+ months (16); and gemcitabine plus docetaxel as first- or second-line, 5.6 months (19). The Duffaud et al abstract (20) showed no statistical difference for PFS between gemcitabine versus (vs.) gemcitabine plus docetaxel as mixed-line therapy (second-line therapy for >77% of patients) (4.9 vs. 6 months).

Response on Imaging

Table 4 also summarizes the outcomes of tumour response on imaging. Three different criteria were used to evaluate tumour response, making a comparison among studies difficult. Omura et al used its own criteria (18); Look et al used the Standard Gynecologic Oncology Group (GOG) response criteria (15); Hensley et al 2002 (19), Hensley et al 2008 (first-line) (17), Hensley et al 2008 (second-line) (16), and the two RCTs from the Duffaud et al abstract (20) used the Response Evaluation Criteria in Solid Tumour (RECIST) (see details under Table 4). The tumour response rate (defined as the sum of the complete response and partial response rate) for each regimen was as follows: doxorubicin as first- or second-line therapy, 25% (95% CI, 9% to 41%) (18); gemcitabine alone as second-line therapy, 21% (CI, 7% to 31%) (15); gemcitabine plus docetaxel as first-line, 36% (CI, 21% to 51%) (17); gemcitabine plus docetaxel as second-line, 27% (CI, 15% to 42%) (16); and gemcitabine plus docetaxel as first- or second-line, 53% (CI, 35% to 70%) (19) in the target patients. The Duffaud et al abstract showed no statistical difference for response rate between gemcitabine alone and gemcitabine plus docetaxel offered as second-line therapy for more than 77% of patients (18% vs. 23%). A lack of specific information on patient characteristics in the abstract, makes it difficult to comment on why the response rate is a little lower than those in the Hensley et al studies. Figure 2 shows the overall response rates by different interventions.

There are no eligible studies that address the question of a differential tumour response rate to chemotherapy between primary pelvic and extra-pelvic metastases in women with uterine LMS.

Table 4. Tumour response rate and survival time for chemotherapy in uterine leiomyosarcoma.

| Study | N for analysis (%) | First or second line therapy | Pretreatment | Dose and schema ^a | CR rate | PR rate | CR+PR rate (95% CI) ^b | SD rate | PD rate | Median OS time (range) | Median PFS time (range) |
|--|--------------------|------------------------------|---|---|---------|---------|--|---------|------------------|--|---|
| Doxorubicin | | | | | | | | | | | |
| Omura 1983 ^c (18) | 28 (68%) | First/second | NR | 60 mg/m ² IV every 3 weeks to a maximum of 480 mg/m ² ; initial doses reduced to 75% if pts had PPR | NR | NR | 25% (9 to 41) | NR | NR | Median 12.1 ^d mo | NR |
| Gem | | | | | | | | | | | |
| Look 2004 ^e (15) | 42 (88%) | Second | 35 (73%) pts received 1-3 chemotherapy regimens; 11 (23%) pts received RT | 1000 mg/m ² Gem IV on days 1, 8, and 15 every 4 weeks to 13 cycles (median 2) | 2% | 19% | 21% (7 to 31) | 17% | 62% | NR | NR |
| Gem+Doc | | | | | | | | | | | |
| Hensley 2002 ^{f,g} (19) | 34 (100%) | First/second | 0-2 chemotherapy regimens; 41% of pts received RT | 900 mg/m ² Gem IV on days 1 and 8, followed by Doc 100 mg/m ² IV on day 8 every 3 weeks up to 8 cycles (median 6); doses reduced to 75% if pts had PPR | 9% | 44% | 53% (35 to 70) | 21% | 26% | 17.9 (95% CI 11.6 to not yet reached) mo | 5.6 (95% CI 4.3 to 9.9) mo |
| Hensley 2008 (second-line) ^f (16) | 48 (94%) | Second | One chemotherapy regimen; 35% of pts received RT | 900 mg/m ² Gem IV on day 1 and 8, followed by Doc 100 mg/m ² IV on day 8 every 3 weeks up to 22 cycles (median 5.5); doses reduced to 75% if pts had PPR | 6% | 21% | 27% (15 to 42) | 50% | 23% | 14.7 (0.8 to 50.9+) mo | 6.7+ (0.7 to 27+) mo |
| Hensley 2008 (first-line) ^f (17) | 42 (100%) | First | No chemotherapy; 29% of pts received RT | 900 mg/m ² Gem IV on day 1 and 8, followed by Doc 100 mg/m ² IV on day 8 every 3 weeks up to 15 cycles (median 4); doses reduced to 75% if pts had previous PPR | 5% | 31% | 36% (21 to 51) | 26% | 38% ^h | 16.1 (4 to 41.3) mo | 4.4 (0.4 to 37+) mo |
| Gem versus Gem+Doc | | | | | | | | | | | |
| Duffaud 2010 [abstract] ^{f,j} (20) | Gem: 22 | Second for >77% of pts | NR | Gem: 1000 mg/m ² IV on day 1, 8, and 15 every 3 weeks in TG Study; 1200 mg/m ² IV on day 1 and 8 every 3 weeks in SARCO02 study | NR | NR | 18% (2 to 34) | NR | NR | NR | 4.9 mo |
| | Gem+Doc : 30 | | | Gem+Doc: 900 mg/m ² Gem IV on day 1 and 8, followed by Doc 100 mg/m ² IV on day 8 every 3 weeks for both studies | NR | NR | 23% (8 to 38) (no significant difference with Gem) | NR | NR | NR | 6 mo (no significant difference with Gem) |

Abbreviations: N = number of patients, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, OS = overall survival, CI = confidence interval, PFS = progression-free survival, NR = not reported, mo = months, pts = patients, PPR = previous pelvic radiation, RT = radiotherapy, Gem = gemcitabine, Doc = docetaxel, TG Study = the French TaxoGem Study, SARC002 study = the Sarcoma Alliance for Research through Collaboration Study 002.

^a Doses might reduce at the next cycle based on toxicity grade and recovery situation.

^b If CI was not provided directly, it was calculated from the data in the studies.

^c Tumour response was assessed by their own criteria. The definition for CR: no evidence of disease for at least one month and did not require surgical documentation; PR: a 50% or greater reduction of the product of perpendicular diameters for at least one month; and PD: a 50% or greater increase in the product of perpendicular diameters of any lesion documented in two separate examinations at least two weeks apart or the appearance of any new lesion within three months of entry into study.

^d The median OS was 12.1 months for 28 ULMS patients with doxorubicin treatment and 20 ULMS patients with doxorubicin plus dimethyl-triazeno-imidazole-carboxamide treatment; since no significant difference between these two groups, we could suppose that the median OS was 12.1 months for 28 patients with doxorubicin treatment.

^e Tumour response was assessed by Standard Gynecologic Oncology Group response criteria. No detail definitions were shown in the original paper, but it was found in another paper (24): CR as the disappearance of all gross evidence of disease for at least 4 weeks; PR as a 50% or greater reduction in the product obtained from measurement of each lesion for at least 4 weeks; PD as a 50% or greater increase in the product obtained from measurement of any lesion documented within 8 weeks of study entry or the appearance of any new lesion within 8 weeks of study entry; SD as any condition not meeting the above criteria. Forty-two pts were evaluable for tumour response. Thus, the denominator of tumour response rate should be “42”. The response rates in Table 2 in the original paper were wrong because “44” was used as a denominator.

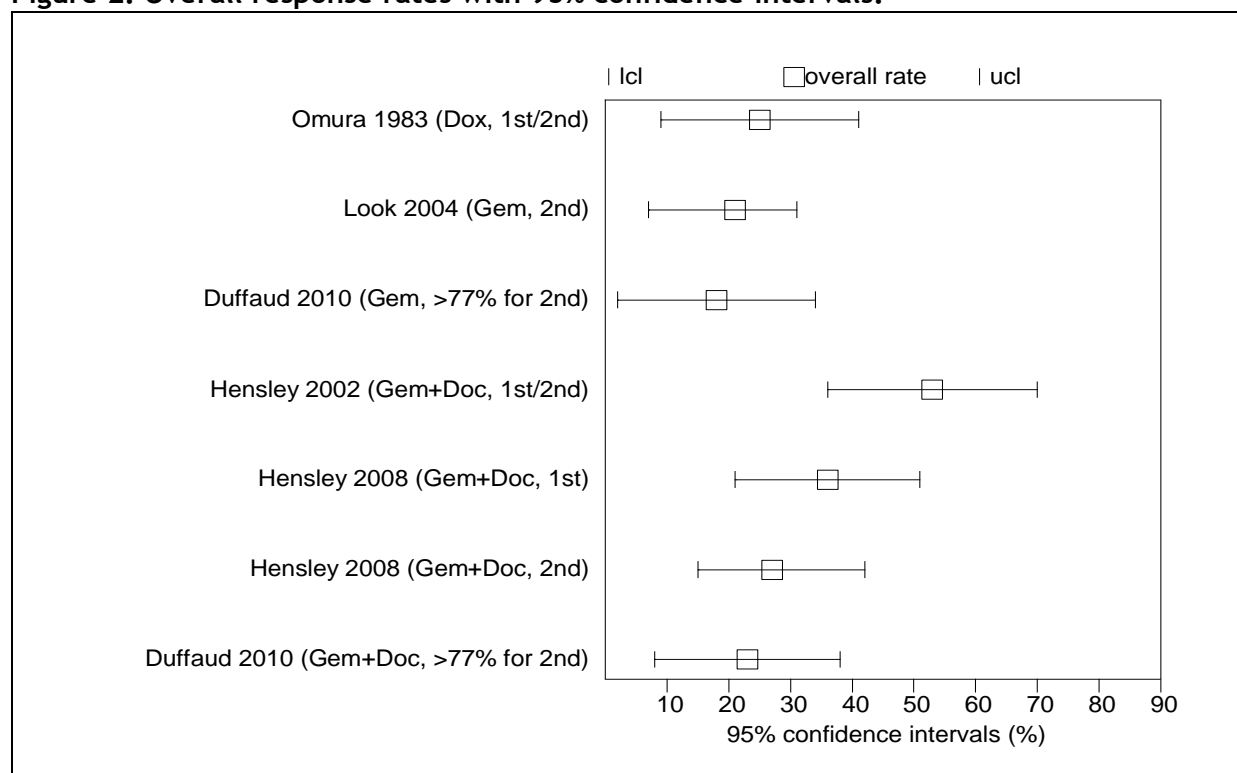
^f Tumour response was assessed by the Response Evaluation Criteria in Solid Tumours. The definition for CR: disappearance of all measurable and nonmeasurable lesions; PR: at least 30% decrease in the sum of the longest diameter of measurable lesions, taking as a reference the baseline sum of the longest diameters of the measurable lesions; PD: at least a 20% increase in the sum of the longest diameter of target lesions, taking as a reference the smallest sum longest diameter recorded since treatment started, or the appearance of new lesions; SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

^g Twenty-nine patients (85%) had uterine leiomyosarcoma and five had other site leiomyosarcoma; one patient was male.

^h Three patients (10%) were not assessed for tumour response, and they were treated as PD patients.

^j A pooled analysis of two RCTs—the French TaxoGem Study and the Sarcoma Alliance for Research Through Collaboration Study 002.

Figure 2. Overall response rates with 95% confidence intervals.



Abbreviations: lcl = lower confidence interval, ucl = upper confidence interval, Dox = doxorubicin, Gem = gemcitabine, Doc = docetaxel, 1st = first-line therapy, 2nd = second-line therapy.

Toxicity

Data on grade 3-4 toxicity are summarized in Table 5. The National Cancer Institute (NCI) common toxicity criteria were used for toxicity grading in three studies (16, 17, 19) and the Standard GOG toxicity criteria in the fourth study (15); the fifth study used its own toxicity criteria (18). Duffaud et al did not report toxicity for the two groups separately.

Hematological toxicity was common for all the regimens, with leucopenia ranging from 14% to 27%, despite the use of recombinant human granulocyte colony-stimulating factor (G-CSF) (16,17,19). For doxorubicin, no patients received red blood cell (RBC) or platelet transfusion, but 3% of the patients developed cardiac toxicity (18). For gemcitabine as the second-line therapy, 9% of the patients received RBC transfusion, 5% had pulmonary toxicity, and 5% had cardiovascular toxicity (15). For gemcitabine plus docetaxel as the second-line therapy, 50% of the patients received RBC and 13% received platelet transfusion, while 8% had pulmonary toxicity (16). For gemcitabine plus docetaxel as the first-line therapy, 43% of the patients received RBC, and 5% received platelet transfusion; 2% had pulmonary toxicity, and 2% developed deep venous thrombosis (17).

ONGOING TRIALS

The NCI clinical trials database (<http://www.cancer.gov/clinicaltrials>) was searched on August 19, 2011 for potential trials meeting the eligibility criteria. Only one arm of an ongoing RCT that investigated the effect of gemcitabine plus docetaxel meet the selection criteria of this systematic review (the first study in Appendix 4). The other eight potentially included studies (Appendix 4) focus on patients with advanced STS and require confirmation of whether a subgroup analysis for 20 or more patients with advanced or recurrent uterine LMS will be included in each study.

DISCUSSION

Only in recent years has uterine LMS been studied uniquely in clinical trials, a result of the observation that uterine LMS can and does respond very differently to various chemotherapeutic agents, compared with LMS arising from other sites (25). Hitherto, uterine LMS was studied in combination with other gynecological sarcomas or was included in STS clinical trials in general. As a consequence, it is not possible to determine (from prospective studies) the natural history or survival of patients with unresectable or metastatic uterine LMS as this has not been uniquely documented in trials with a no-treatment or placebo control. The Omura et al study established doxorubicin alone as an acceptable standard of care in this population, and this has remained the status quo for the past 30 years (18). Additionally, one CCO clinical guideline (updated in 2011) has recommended that single-agent doxorubicin remains the standard of care for patients with STS, including women with uterine LMS (5). Recent single-arm studies, however, have demonstrated high response rates to newer cytotoxics. In Table 4 and Figure 2, the combination of gemcitabine plus docetaxel offers a tumour response rate of 27% to 53% compared with 25% for doxorubicin alone or 21% for gemcitabine alone, as first- or second-line therapy. Compared with tumour response rate, OS or PFS is a more important clinical outcome for cancer patients. The studies of gemcitabine plus docetaxel have resulted in numerically longer median OS (14.7-17.9 months) than that reported in the study of doxorubicin alone (12.1 months) in Table 4. Whether gemcitabine alone can improve patients' survival is unclear because the unique eligible study for gemcitabine alone did not report OS or PFS information (15). However, more patients had grades 3-4 hematological toxicity in the combination of gemcitabine plus docetaxel studies compared with gemcitabine or doxorubicin alone (Table 5). For example, 43% to 50% of patients received RBC transfusion compared with 9% in the gemcitabine-alone study. Furthermore, the Duffaud et al abstract (20) that pooled the individual patient data of uterine LMS patients from two RCTs did not find a statistically significant difference for median PFS and response rate (Table 4) between gemcitabine plus docetaxel versus gemcitabine alone.

There are no fully-published RCTs or good-quality comparative clinical trials that compare the efficacy of any two regimens among gemcitabine, gemcitabine plus docetaxel, or trabectedin in patients with inoperable, locally advanced, recurrent, or metastatic uterine LMS. It is difficult to make any substantive conclusions about each regimen due to the confounders of prior pelvic radiation, first- versus second-line therapy, and use of granulocyte growth factors. No treatment option can be recommended over the others. Once published, the French TaxoGem study (an RCT comparing the effect of gemcitabine alone with gemcitabine plus docetaxel) will offer more information on this point (21).

There is insufficient evidence to support or against the use of trabectedin in advanced or relapsed uterine LMS patients. However, three ongoing RCTs will compare doxorubicin with trabectedin with or without doxorubicin (the first three trials in Appendix 4), and one ongoing RCT will test the continuing versus intermittent trabectedin-regimens (the fourth trial in Appendix 4) in patients with advanced STS. There are no ongoing eligible studies that address the question of a differential tumour response rate to chemotherapy between recurrent pelvic disease and extra-pelvic metastases in women with uterine LMS.

Table 5. Grades 3-4 toxicity from chemotherapy in uterine leiomyosarcoma

| Study | N for analysis (%) | Protecting agent | Haematological toxicity | Gastrointestinal toxicity | Other main toxicity |
|--|--------------------|--|--|------------------------------------|--|
| Doxorubicin | | | | | |
| Omura 1983 ^{a,b} (18) | 90 (75%) | NR | Leucopenia: 16%; thrombocytopenia: 4% | 2% | Questionable cardiac toxicity: 3% (no detail) |
| Gemcitabine | | | | | |
| Look 2004 ^c (15) | 44 (92%) | NR | Leucopenia: 27%; neutropenia: 34%; thrombocytopenia: 11%; anaemia: 7%; RBC transfusion: 9%. | Nausea or vomiting: 9%; others: 5% | Neurotoxicity: 5%; pulmonary toxicity (might be not related to drug): 5%; dermatological toxicity: 5%; cardiovascular toxicity: 5% (no detail) |
| Gemcitabine + Docetaxel | | | | | |
| Hensley 2002 ^d (19) | 34 (100%) | RHGCSF 150 µg/m ² on day 9-15 per cycle subcutaneously; recommended dexamethasone 8 mg bid orally starting the day before docetaxel and continuing for 3 days | Neutropenia: 21%; neutropenic fever: 6%; thrombocytopenia: 29%; anaemia: 15%. | Diarrheal: 12% | Dyspnea: 21%; sensory neuropathy: 6%; docetaxel allergy: 3%; venous thrombosis: 3%; fatigue: 21%. |
| Hensley 2008 (second-line) ^d (16) | 48 (94%) | RHGCSF 150 µg/m ² on day 9-15, or pegfigrastim 6 mg on day 9-10 subcutaneously; recommended dexamethasone 8 mg bid orally starting the day before docetaxel and continuing for 3 days per cycle | Leucopenia: 23%; neutropenic fever: 4%; thrombocytopenia: 40%; anaemia: 25%; haemorrhage: 2%; RBC transfusion: 50%; platelet transfusion: 13%. | 6% | Fluid retention syndrome: 19%; constitutional symptoms: 10%; pulmonary toxicity (none was drug related): 8%; fatigue: 2%. |
| Hensley 2008 (first-line) ^d (17) | 42 (100%) | RHGCSF 150 µg/m ² on day 9-15, or pegfigrastim 6 mg on day 9-10 subcutaneously; recommended dexamethasone 8 mg bid orally starting the day before docetaxel and continuing for 3 days per cycle | Leucopenia: 14%; thrombocytopenia: 14%; anaemia: 24%; RBC transfusion: 43%; platelet transfusion: 5%. | Nausea: 14% | Neurotoxicity: 2%; cardiovascular toxicity: 2% (no detail); pulmonary toxicity: 2%; docetaxel allergy: 2%; deep venous thrombosis: 2%; fatigue: 17%. |

Abbreviations: N = number of patients, NR = not reported, RBC = red blood cell, RHGCSF = recombinant human granulocyte colony-stimulating factor.

^a Adverse effects were assessed by their own criteria. The definition of grades 3 and 4 toxicity were 1000-1999/mm³ and <1000/mm³ for leukocyte; 25,000 - 49,000 and <25,000 for platelets; vomiting not prevented by antiemetic.

^b Toxicities were reported among 120 various histological subtypes of uterine sarcoma patients with doxorubicin.

^c Standard Gynecologic Oncology Group response criteria were used for toxicity grading (no detail definitions were shown in the original paper).

^d The National Cancer Institute Common Toxicity criteria were used for toxicity grading (no detail definitions were shown in the original paper).

CONCLUSIONS

Doxorubicin, gemcitabine, and gemcitabine plus docetaxel are options for the treatment of women with inoperable, locally advanced, recurrent, or metastatic uterine LMS as first- or second-line therapy. Hematological toxicity and other toxicities such as neurotoxicity, pulmonary and cardiovascular toxicity should be monitored. G-CSF support is recommended when gemcitabine plus docetaxel is employed. Well-designed and good-quality RCTs are required to investigate the efficacy of chemotherapy and QOL, and differential tumour response rates to chemotherapy, between recurrent pelvic compared with extra-pelvic metastases in patients with uterine LMS.

CONFLICT OF INTEREST

The conflict of interest details are shown at the end of Section 3.

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For a complete list of the Sarcoma DSG and the Gynecology Cancer DSG members, please visit the CCO website at <http://www.cancercare.on.ca>.

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Appendix 1. Working Group, Sarcoma DSG, and Gynecology Cancer DSG members.

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ARCHIVED

Appendix 2. Search strategy in MEDLINE for 11-11 (June 17, 2011).

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present

Search Strategy:

| # | Searches | Results |
|----|--|---------|
| 1 | (gemcitabine or gemzar or (docetaxel or taxotere)).mp. | 13800 |
| 2 | (doxorubicin or adriamycin or trabectedin or ecteinascidin\$ or ET-743 or yondelis).mp. | 45588 |
| 3 | 1 or 2 | 58005 |
| 4 | (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt. | 1518477 |
| 5 | (case report\$ or editorial\$ or comment\$ or letter\$).pt. | 2483273 |
| 6 | 4 or 5 | 2885388 |
| 7 | exp Sarcoma/ or sarcoma\$.mp. | 133150 |
| 8 | (leiomyosarcoma\$ or LMS or L-sarcoma).mp. | 9793 |
| 9 | 7 or 8 | 134990 |
| 10 | (3 and 9) not 6 | 3364 |
| 11 | limit 10 to (english language and humans and yr="2004 -Current") | 720 |

Appendix 3. Search strategy in EMBASE for 11-11 (June 17, 2011).

Database(s): Embase 1996 to 2011 Week 23

Search Strategy:

| # Searches | Results |
|---|---------|
| 1 (gemcitabine or gemzar or (docetaxel or taxotere)).mp. | 37394 |
| 2 (doxorubicin or adriamycin or `trabectedin or ecteinascidin\$ or ET-743 or yondelis).mp. | 71629 |
| 3 (editorial or note or letter erratum or short survey or abstract).pt. or abstract report/ or letter/ or case study/ | 1691928 |
| 4 1 or 2 | 98364 |
| 5 sarcoma\$.mp. or exp sarcoma/ | 68953 |
| 6 (leiomyosarcoma\$ or LMS or L-sarcoma).mp. | 6706 |
| 7 5 or 6 | 70234 |
| 8 (4 and 7) not 3 | 7539 |
| 9 limit 8 to (human and english language and yr="2004 -Current") | 4328 |

Appendix 4. Ongoing trials.

1. A Study of the Safety and Effectiveness of Trabectedin Versus Doxorubicin-based Chemotherapy in Patients With Translocation-Related Sarcomas

Phase: Phase III RCT

Status: Active

Age: 18 and over

Sponsor: Pharmaceutical / Industry

Protocol IDs: CR015769, ET-C-002-07, NCT00796120

Estimated sample size: 80

Study start date: November 2008

Summary

The purpose of this study is to evaluate the effectiveness of trabectedin compared to standard doxorubicin-based chemotherapy as first-line treatment in patients with advanced Translocation-Related Sarcomas.

2. Phase IIB/III Randomized Study of Doxorubicin Hydrochloride Versus Trabectedin in Patients With Previously Untreated Advanced or Metastatic Malignant Soft Tissue Sarcoma

Phase: Phase III RCT, Phase II

Status: Active

Age: 18 and over

Sponsor: Other, Pharmaceutical / Industry

Protocol IDs: EORTC-62091, EORTC 62091, TRUSTS, EUDRACT-2009-014889-26, EU-21059, PMAR-EORTC-62091, SARC-020, NCT01189253

Estimated sample size: 370

Expected completion: December 2012

Summary

--To evaluate whether trabectedin given as first-line chemotherapy for patients with previously untreated advanced or metastatic malignant soft tissue sarcoma prolongs progression-free survival as compared to doxorubicin hydrochloride.

--To identify and validate biomarkers (including, but not limited to, XPG, BRCA1, RAD51, BRCA2, ATM and CHK1) of sensitivity to trabectedin in order to allow the selection of patients that benefit most from trabectedin treatment. (Optional translational research).

3. Clinical Trial Of Doxorubicin Versus Trabectedin Plus Doxorubicin In The First Line Treatment Of Patients With Advanced Non Operable And/Or Metastatic Soft Tissue Sarcomas

Phase: Phase II RCT

Status: Active

Age: 18 to 70

Sponsor: Other

Protocol IDs: GEIS-20, 2008-008922-55, NCT01104298

Estimated sample size: 182

Expected completion: December 2012

Summary

--The proposed investigation intends to explore if the combination of trabectedin and doxorubicin in the first line of treatment of advanced sarcomas obtains better results than doxorubicin monotherapy. This proposal arises from the need to bring to the first line of treatment of advanced STS agents that have shown activity in second line. The goal is to improve available standard treatments. Tumors in patients not previously exposed to chemotherapy have not been selected in their biological behavior and they are the best scenario to test antitumor activity of a new anticancer drug.

--The combination of drugs with different mechanisms of action may be a clear advantage to obtain better results and potential synergy. On the other hand, the toxicity profiles of both study drugs are different and worsening or summative of adverse effects is not expected.

--The purpose of this study is to determine the efficacy of the combination of trabectedin and doxorubicin in comparison with doxorubicin alone in patients with advanced non operable and/or metastatic Soft Tissue Sarcomas (STS).

4. Continuing vs Intermittent Trabectedin-regimen in Patients With Advanced Soft Tissue Sarcoma Experiencing Response or Stable Disease After the 6th Cycle

| |
|--|
| <p>Phase: Phase II RCT Status: Active Age: 18 and over Sponsor: Other Protocol IDs: T-DIS-1001, NCT01303094 Estimated sample size: 50 Expected completion: February 2017 Summary This randomization discontinuation trial will allow for concomitant evaluation of the following: --Side effects and benefits of immediate continuation of Trabectedin after the sixth cycle --Side effects and benefits of a drug holiday</p> |
| <p>5. Phase III Randomized Study of Gemcitabine Hydrochloride and Docetaxel With or Without Bevacizumab in Patients With Advanced or Recurrent Uterine Leiomyosarcoma Phase: Phase III RCT Status: Active Age: 18 and over Sponsor: NCI Protocol IDs: GOG-0250, NCT01012297 Estimated sample size: 130 Expected completion: January 2015 Summary --To determine whether the addition of bevacizumab to fixed-dose rate gemcitabine hydrochloride and docetaxel reduces the progression-free survival event rate when compared with gemcitabine hydrochloride and docetaxel plus placebo in patients with advanced or recurrent uterine leiomyosarcoma (LMS). --To determine the objective response rate, as measured by RECIST criteria, in patients treated with fixed-dose rate gemcitabine hydrochloride and docetaxel with bevacizumab compared with the objective response rate of patients treated with fixed-dose rate gemcitabine hydrochloride and docetaxel with placebo. --To determine if the addition of bevacizumab to the combination of gemcitabine hydrochloride and docetaxel increases overall survival of patients with advanced or recurrent uterine LMS. --To determine the toxicity profile of fixed-dose rate gemcitabine hydrochloride and docetaxel with and without bevacizumab in this patient population. --To bank formalin-fixed and paraffin-embedded tumor tissue for research. A Study of Trabectedin or Dacarbazine for the Treatment of Patients With Advanced L-sarcoma Phase: Phase III RCT Status: Approved-not yet active Age: 15 and over Sponsor: Pharmaceutical / Industry Protocol IDs: CR018004, ET743SAR3007, NCT01343277 Estimated sample size: 570 Expected completion: April 2014 Summary The purpose of this study is to evaluate whether overall survival for the trabectedin group is superior to the dacarbazine group for patients with advanced L-sarcoma (liposarcoma or leiomyosarcoma) who were previously treated with an anthracycline and ifosfamide.</p> |
| <p>6. Trofosfamide Versus Adriamycin in Elderly Patients With Soft Tissue Sarcoma Phase: Phase II RCT Type: Treatment Status: Active Age: 60 and over Sponsor: Other Protocol IDs: jth_001, NCT00204568 Estimated sample size: 117 Expected completion: June 2011</p> |

Summary

The goal of this trial is to determine whether oral continuous (metronomic) therapy with trofosfamide results in a similar rate of progression-free time after 6 months as intravenous treatment with adriamycin. In addition, the study is intended to investigate the level of toxicity associated with the two treatment regimens (safety profile).

7. Evaluation of Side Effects and Relative Activity of Two Chemotherapy Regimens in the Treatment Soft Tissue Sarcoma

Phase: Phase II RCT

Status: Active

Age: 10 and over

Sponsor: Other

Protocol IDs: UMCC 2004.010, NCT00189137

Estimated sample size: 80

Expected completion: June 2015

Summary

The purpose of this study is to explore how a sarcoma is affected by and the side effects of a newer combination of chemotherapy drugs (gemcitabine and docetaxel) as compared to a standard combination of chemotherapy drugs, ifosfamide and doxorubicin.

8. A Study of Trabectedin or Dacarbazine for the Treatment of Patients With Advanced L-sarcoma

Phase: Phase III RCT

Status: Approved-not yet active

Age: 15 and over

Sponsor: Pharmaceutical / Industry

Protocol IDs: CR018004, ET743SAR3007, NCT01343277

Estimated sample size: 570

Expected completion: April 2014

Summary

The purpose of this study is to evaluate whether overall survival for the trabectedin group is superior to the dacarbazine group for patients with advanced L-sarcoma (liposarcoma or leiomyosarcoma) who were previously treated with an anthracycline and ifosfamide.

9. Phase III Randomized Study of Doxorubicin With Versus Without Ifosfamide and Pegfilgrastim in Patients With Locally Advanced or Metastatic Soft Tissue Sarcoma

Phase: Phase III RCT

Status: Closed

Age: 18 to 60

Sponsor: Pharmaceutical / Industry

Protocol IDs: EORTC-62012, NCT00061984

Estimated sample size: 450

Study start date: April 2003

Summary

--Compare the progression-free and overall survival of patients with locally advanced or metastatic soft tissue sarcoma treated with doxorubicin with vs without ifosfamide and pegfilgrastim as first-line therapy.

--Compare the response in patients treated with these regimens.

--Compare the treatment-related mortality of patients treated with these regimens.

--Compare the toxicity of these regimens in these patients.

Abbreviation: RCT = randomized controlled trial.

**A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)**

**Chemotherapy (i.e., Gemcitabine, Docetaxel Plus Gemcitabine,
Doxorubicin, or Trabectedin) for Inoperable, Locally Advanced,
Recurrent, or Metastatic Uterine Leiomyosarcoma:
Development Methods, Recommendation Development
and External Review Process**

*A. Gupta, X. Yao, S. Verma, H. Mackay, L. Hopkins,
the Sarcoma Disease Site Group (DSG), and the Gynecology Cancer DSG*

Report Date: July 18, 2012

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is comprised of three sections:

- *Section 1: Guideline Recommendations.* Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.

- *Section 2: Evidentiary Base.* Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process.* Summarizes the EBS development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This EBS was developed by the Sarcoma and Gynecology DSGs of the CCO PEBC. The series is a convenient and up-to-date source of the best available evidence on chemotherapy (i.e., gemcitabine, docetaxel plus gemcitabine, doxorubicin, or trabectedin) for inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma, developed through a review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario.

Report Approval Panel

Prior to the submission of this EBS draft report for external review, the report was reviewed and approved by the PEBC Report Approval Panel (RAP), which consists of three members, including two oncologists, with expertise in clinical and methodology issues, and a methodologist. The key issues raised by the RAP are below, followed by the bulleted modifications and/or responses made by the guideline authors:

1. The second research question is unclear and may be changed to “Is there a difference in the response rate to the various chemotherapy options for LMS [gemcitabine, gemcitabine plus docetaxel, doxorubicin, or trabectedin] in patients with recurrent pelvic disease or extra-pelvic metastases”.
 - We changed the second research question to “Is there a difference in tumour response rate to chemotherapy (i.e., gemcitabine, gemcitabine plus docetaxel, doxorubicin, or trabectedin) between recurrent pelvic disease compared with extra-pelvic metastases in patients with uterine LMS?”.
2. Although the evidence is somewhat conflicting, the combination of gemcitabine and docetaxel is not clearly superior to gemcitabine alone and appears to have significantly more toxicity. It does not appear that the authors took account of the greater toxicities with the combination in making the recommendation the 50% transfusion a requirement alone with the combination is a very significant difference from the toxicity profile of gemcitabine.
 - First, we realized that the combination of gemcitabine plus docetaxel had more toxicity than did doxorubicin alone or gemcitabine alone, but led to the numerically longer median OS than that reported in the study of doxorubicin alone (14.7-17.9 vs. 12.1 months). Second, the undertaking of an RCT to compare gemcitabine plus docetaxel with doxorubicin alone (the standard treatment) may be unlikely; therefore, recommendations regarding gemcitabine plus docetaxel heavily rely on phase II trial data. Third, the eligible study that investigated the effect of gemcitabine alone reported only the tumour response rate (21%, which is not better than 25% compared with doxorubicin alone) and did not report the OS or PFS, results that are more important outcomes for cancer patients. Fourth, although an abstract pooling data from two RCTs failed to demonstrate the superiority of gemcitabine plus docetaxel over gemcitabine alone for tumour response rate and PFS; recommendations cannot be made based on published abstracts because some published abstracts may have methodological flaws and

- would never be fully published. Fifth, without fully published RCTs or good-quality comparative studies, no single treatment option can be recommended over others. After discussion, the guideline authors felt the benefits from the combination of gemcitabine plus docetaxel are potentially substantial for the targeted patients, prolonging their lives, in contrast to having more toxicities when using doxorubicin alone or gemcitabine alone. Thus, the combination of gemcitabine plus docetaxel is still an option for the targeted patients to date. However, it is more appropriate to change “is” to “may be” in the recommendations (Doxorubicin or gemcitabine alone or gemcitabine plus docetaxel may be treatment options as first- and/or second-line therapy for women with inoperable, locally advanced, recurrent, or metastatic uterine LMS.), and to add more discussions under Section 1. Justification for Recommendation in and under Section 2. Discussion part in to support our conclusion more effectively.
3. The comments about toxicity should be expanded. In particular, the degree of anemia with the gemcitabine-docetaxel combination should be commented upon. Similarly, the recommendation states that pulmonary and cardiovascular toxicity should be monitored. It would be helpful to state the incidence of cardiotoxicity that has been identified in the studies and expand in the toxicity section on what is meant by cardiovascular toxicity.
 - More toxicity details have been added in a table under Section 1. Key Evidence in response to the reviewer’s comment. There is no detail about cardiotoxicity in the original studies.
 4. It’s not clear why the FDA [US Food and Drug Administration] approved it. The rationale for the approval by the FDA of the gemcitabine-docetaxel combination is not provided. This would be useful for the readers to know.
 - We do not know why the FDA approved the combination of gemcitabine plus docetaxel in uterine LMS. Thus, we deleted that sentence under Section 1. Justification for Recommendation.
 5. RAP members concerned if there were more evidence to support that doxorubicin is the standard except the Omura study only.
 - Uterine LMS were studied in combination with other gynecological sarcomas or were included in STS clinical trials in general. Only in recent years has uterine LMS been studied uniquely in clinical trials. Please see the first paragraph under the Section 2. Discussion. An updated 2011 CCO guideline recommended that doxorubicin alone remains the standard of care for patients with advanced STS, including women with uterine LMS. To make this point clearer, we added the updated CCO guideline as a reference under Section 1. Justification for Recommendation and under Section 2. Introduction.
 6. The sentence “It is difficult to make any substantive conclusions regarding the relative toxicities (especially haematological toxicity) of each regimen due to the confounders of prior pelvic radiation, first- vs. second-line therapy, and use of granulocyte growth factors.” is confused. It would be useful if the authors could either add a statement of why we ought to believe the benefits data more than the toxicities data or reconsider the framing of the recommendations.
 - We accept the reviewer’s comments and have changed the above sentence in the Section 2. Discussion. We added more discussion to balance the benefits and harms of these chemotherapy agents. Please see the above details from the authors’ response in Comment 2.
 7. All the information is there in Section 1 but the bullets are very wordy and tough to follow. For examples, Recommendations, first bullet: the sentence should finish with

"based on..."; Key Evidence, Bullets 3, 4 and 5 would be best served by a table (a simplified version of Table 4 maybe) since it's very difficult for the reader to get through all the verbiage.

- We accept the reviewer's comments and have provided a new table to replace bullets 3 through 6 under Section 1. Key Evidence, as well as various changes to make Section 1 clearer and more concise.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two pronged and includes a targeted peer review intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Guideline Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC Report Approval Panel, the guideline authors circulated Sections 1 and 2 to external review participants for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the guideline authors.

BOX 1:

DRAFT RECOMMENDATIONS (approved for external review March 19, 2012)

QUESTIONS

1. Does chemotherapy (i.e., gemcitabine, gemcitabine plus docetaxel, doxorubicin, or trabectedin) improve clinical outcomes (i.e., tumour response rate, progression-free survival [PFS], overall survival [OS], toxicity, or quality of life [QOL]) in women with inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma (LMS)?
2. Is there a difference in tumour response rate to chemotherapy (i.e., gemcitabine, gemcitabine plus docetaxel, doxorubicin, or trabectedin) between recurrent pelvic disease compared with extra-pelvic metastases in patients with uterine LMS?

TARGET POPULATION

Women with inoperable, locally advanced, recurrent, or metastatic uterine LMS.

INTENDED USERS

Medical oncologists, gynecologic oncologists, general surgeons, radiation oncologists, pharmacists, and other clinicians who take care of the above target patients.

RECOMMENDATIONS AND KEY EVIDENCE

In the absence of randomized controlled trials (RCTs) comparing chemotherapy with no treatment controls for inoperable, recurrent, or metastatic LMS of the uterus, the Sarcoma DSG and Gynecologic Cancer DSG offer the following recommendations:

- Doxorubicin alone or gemcitabine alone or gemcitabine plus docetaxel may be treatment options as first and/or second line therapy for women with inoperable, locally advanced, recurrent, or metastatic uterine LMS, based on current available evidence from the medical literature (four single-arm phase II studies, one arm of an RCT, and one abstract).
 - Hematological toxicity is common, and granulocyte growth factor (G-CSF) should be considered when gemcitabine plus docetaxel is used.
 - Pulmonary and cardiovascular toxicity should be monitored.

- No recommendation is made for or against using trabectedin in the targeted patients.
- Patients should be encouraged to participate in clinical trials testing novel or targeted approaches in this disease.

Q Qualifying Statement

- The following chemotherapy agent doses were suggested from the included studies:
 - Doxorubicin: 60-80 mg/m² intravenously (IV) every 3 weeks;
 - Gemcitabine: 1000 mg/m² IV on days 1, 8, and 15 every 4 weeks;
 - Gemcitabine plus docetaxel: gemcitabine 900 mg/m² IV on days 1 and 8, followed by docetaxel 100 mg/m² IV on day 8 every 3 weeks.

Key Evidence

- There are no trials of high methodological quality that document the outcomes of patients with advanced or metastatic uterine LMS when no systemic therapy is employed. Doxorubicin has been considered a ‘standard of care’ for over 30 years.
- Survival and response rate and toxicity for each regimen are shown below:

| Chemotherapy | | 1 st /2 nd line therapy | Median OS | Median PFS | Response rate (CR+PR) | Grades 3-4 toxicity |
|--------------------------------|---------|---|--------------|------------|--------------------------------------|---|
| Doxorubicin ^a (1) | | 1 st /2 nd | 12.1 mo | NR | 25% (95% CI, 9-41%) | Leucopenia: 16%, thrombocytopenia: 4%; Questionable cardiac toxicity: 3% (no detail) |
| Gem ^b (2) | | 2 nd | NR | NR | 21% (CI, 7-31%) | Leucopenia: 27%, thrombocytopenia: 11%, RBC transfusion: 9%; Neurotoxicity: 5%; Pulmonary toxicity: 5%; Cardiovascular toxicity: 5% (no detail) |
| Gem+Doc ^c (3-5) | | 1 st /2 nd | 14.7-16.1 mo | 4.4-6.7 mo | 27% (CI, 15-42%) to 53% (CI, 35-70%) | Leucopenia: 14-23%, thrombocytopenia: 14-40%, RBC transfusion: 43-50%; Neurotoxicity: 0-6%; Pulmonary toxicity: 0-8% |
| Gem vs. Gem+Doc (abstract) (6) | Gem | 1 st /2 nd | NR | 4.9 mo | 18% (CI, 2-34%) | NR |
| | Gem+Doc | 1 st /2 nd | NR | 6.0 mo | 23% (CI, 8-38%) | NR |

Abbreviations: OS = overall survival, PFS = progression-free survival, CR = complete response, PR = partial response, CI = confidence interval, NR = not reported, mo = months, Gem = gemcitabine, RBC = red blood cell, Doc = docetaxel, vs. = versus.

^a Adverse effects were assessed by their own criteria.

^b Standard Gynaecologic Oncology Group response criteria were used for toxicity grading.

^c The National Cancer Institute Common Toxicity criteria were used for toxicity grading.

- To date, there is insufficient evidence to support or refute the use of trabectedin in the targeted patients.
- There was no data on differences in response between recurrent pelvic disease and extra-pelvic metastases, or on QOL.

Justification for Recommendation

Doxorubicin alone has long been considered a standard treatment for patients with inoperable, locally advanced, recurrent, or metastatic soft tissue sarcoma (STS), including women with uterine leiomyosarcoma (7, 8).

The studies included in this systematic review must have reported at least one relevant outcome on 20 or more targeted patients. If studies did not perform subset analyses for uterine LMS, they were excluded.

Although the Omura et al 1983 study used a dose of 60 mg/m² IV every 3 weeks for doxorubicin, this study was conducted almost 30 years ago, and a dose of 70-80 mg/ m² IV every 3 weeks has usually been used for locally advanced or metastatic STS since 1990 (9). Thus, the suggested dose for doxorubicin is 60 to 80 mg/m² IV every 3 weeks in the Qualifying Statement.

From single-arm studies, the studies of gemcitabine plus docetaxel have reported numerically longer median OS (14.7-17.9 months) than that reported in the study of doxorubicin alone (12.1 months), but it seems clear that the combination of gemcitabine plus docetaxel resulted in more toxicity than did doxorubicin alone. As there has been no randomized comparison of these options, no conclusions can be made regarding the superiority of gemcitabine plus docetaxel compared with doxorubicin. It is unlikely that such a comparative study will be undertaken; therefore, recommendations regarding gemcitabine plus docetaxel rely heavily on phase II trial data. The only available study for single-agent gemcitabine reported a tumour response rate of 21%, which is not better than 25% compared with doxorubicin alone, and did not report the OS or PFS information. Thus, it is unclear from this study whether gemcitabine alone can improve survival or PFS for the targeted patient. The only randomized data available from an abstract (pooled data from two RCTs) (6) failed to demonstrate the superiority of gemcitabine plus docetaxel over gemcitabine alone for tumour response rate and PFS, and provided no information about OS. However, the recommendations can not be made based on published abstracts. Without fully published RCTs or good-quality comparative studies, and after considering the balance between the benefits and harms from these chemotherapeutic agents, one treatment option cannot be recommended over the others (see additional discussion in Section 3, pages 2-4). Gemcitabine plus docetaxel is not currently funded by Cancer Care Ontario.

FUTURE RESEARCH

After searching the National Cancer Institute (NCI) clinical trials database (<http://www.cancer.gov/clinicaltrials>) on August 19, 2011 for ongoing trials, only one arm of an ongoing RCT that investigated the effect of gemcitabine plus docetaxel met the selection criteria for this systematic review. The other eight potentially included studies focus on patients with advanced STS and require confirmation of whether a subgroup analysis for 20 or more patients with advanced or recurrent uterine LMS will be included for each study. There are no eligible studies that address any differences in tumour response rate between pelvic and extra-pelvic metastases in patients with uterine LMS. Thus, there is a need for well-designed and good-quality RCTs to investigate the efficacy of chemotherapy in patients with inoperable, locally advanced, recurrent, or metastatic uterine LMS.

Methods

Targeted Peer Review: During the guideline development process, 10 targeted peer reviewers from the North America to be clinical and/or methodological experts on the topic were identified by the guideline authors. Several weeks prior to completion of the draft report, the

nominees were contacted by email and asked to serve as reviewers. Three reviewers agreed, and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on March 23, 2012. Follow-up reminders were sent at two weeks and at four weeks. All the targeted peer reviewers were required to complete the conflict of interest form.

Professional Consultation: 65 potential participants were identified by the guideline authors. Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on March 23, 2012. Two follow-up reminders were sent on April 9 and April 23, 2012.

Results

Targeted Peer Review: Responses were received from three of four reviewers: Suzie Lau from Montreal Quebec, Ursula Lee from Vancouver British Columbia, and Richard Tozer from Hamilton Ontario. The key results of the feedback survey are summarized in Table 1. The written comments by targeted peer reviewers and the modifications/actions/responses taken by the authors are summarized in Table 2.

Table 1. Responses to nine items on the targeted peer reviewer questionnaire.

| Question | Reviewer Ratings (n=3) | | | | |
|--|---|-----|----------------|-----|------------------------|
| | Lowest Quality (1) | (2) | (3) | (4) | Highest Quality (5) |
| 1. Rate the guideline development methods. | 0 | 0 | 0 | 2 | 1 |
| 2. Rate the guideline presentation. | 0 | 0 | 0 | 0 | 3 |
| 3. Rate the guideline recommendations. | 0 | 0 | 0 | 1 | 2 |
| 4. Rate the completeness of reporting. | 0 | 0 | 0 | 1 | 2 |
| 5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing? | 0 | 0 | 0 | 2 | 1 |
| 6. Rate the overall quality of the guideline report. | 0 | 0 | 0 | 1 | 2 |
| | Strongly Disagree (1) | (2) | Neutral (3) | (4) | Strongly Agree (5) |
| 7. I would make use of this guideline in my professional decisions. | 0 | 0 | 0 | 1 | 2 |
| 8. I would recommend this guideline for use in practice. | 0 | 0 | 0 | 1 | 2 |
| 9. What are the barriers or enablers to the implementation | <ul style="list-style-type: none"> I would suggest always offering clinical trials as a viable alternative beyond the first and second line setting. | | | | |

| | |
|---------------------------|--|
| of this guideline report? | <ul style="list-style-type: none"> • Trabectin is not readily available in North America. • Neither gemcitabine nor docetaxel are funded via the NDFP in Ontario for this indication. (Nevertheless neither are particularly expensive these days and given the relative rarity of the clinical scenario, this really is not an insurmountable barrier). |
|---------------------------|--|

Table 2. Summary of written comments by targeted peer reviewers and the modifications/actions/responses regarding written comments.

| Summary of written comments | Modifications, actions, or responses |
|---|---|
| 1. I suppose that is due to lack of studies, no cost analysis was possible but a quick mention that this was considerable would be helpful. | Analysis of costs is beyond the scope of this guideline. |
| 2. The literature is available for first and second line treatment but this population of patients will likely go to at least third line treatment. Is there a hint of trabectedin demonstrating some effectiveness in this setting? | Up to date, there is no evidence about the efficacy of trabectedin in the target patient population, which met this guideline study selection criteria. |
| 3. The recommendations don't really answer the primary question and I think it might be better to re-phrase the question. The question asked is "Does chemo improve outcomes?". The answer is: We are not sure because there have been no well done RCT of chemo vs no chemo. You do answer this question but it is not prominent in the guideline text. So then the next question should be , "In the absence of RCT of no chemo, what is the recommendation for first or second line chemo and what is the evidence". The guideline spends all its time answering this question , which it does well. In regards to the second question, I'm not sure it should be included in this set of guidelines as you have no answer as there is no evidence to speak of. | Good point! Before the systematic review was done, it was unknown what kind evidence would be found. The goal of this guideline is to investigate the effect of gemcitabine, gemcitabine plus docetaxel, doxorubicin, or trabectedin, and what are their toxicities in women with inoperable, locally advanced, recurrent, or metastatic uterine LMS. Thus, we could change the first research question to "What are the effectiveness of chemotherapy (i.e., doxorubicin, gemcitabine, gemcitabine plus docetaxel, or trabectedin in women with inoperable, locally advanced, recurrent, or metastatic uterine LMS and what is the difference about toxicity among these chemotherapy agents?" To date there is no evidence to answer the second research question. We think it is a meaningful research question worth keeping for the next updating of the literature search. |
| 4. I'm not sure how exhaustive you want to be viz-a-viz evidence and recommendations. For eg, do you want to include other potential treatments (eg, combinations of Doxo plus cyclo or Ifos or Dacarbazine) but summarize the data to say no studies have shown improvement in survival for combination vs Doxorubicin alone. As well, do you want to mention the role, if any, for | This review focused on the most common regimens used to treat women with advanced unresectable uterine LMS. There are likely other combinations of chemotherapy used ('plus doxorubicin', for instance); however, we did not feel these were used enough to warrant formal review. If there were evidence to support the effectiveness of trabectedin in women with |

| | |
|--|---|
| Caelyx. Finally, I'm not sure why Trabectedin was included when it is not readily available in North America. | inoperable, locally advanced, recurrent, or metastatic uterine LMS, it might be possible to obtain funding for such a study in North America. |
|--|---|

Professional Consultation: Nineteen of 65 (29%) responses were received. Ten stated that they did not have interest in this area. The key results of the feedback survey from nine doctors are summarized in Table 3. The comments from the professional consultants and the Working Group modifications/actions taken in response are summarized in Table 4.

Table 3. Responses to four items on the professional consultation survey.

| Question | Number (%) | | | | |
|--|--|-----|-----|-----|---------------------|
| | Lowest Quality (1) | (2) | (3) | (4) | Highest Quality (5) |
| 1. Rate the overall quality of the guideline report. | 0% | 11% | 11% | 67% | 11% |
| | Strongly Disagree (1) | (2) | (3) | (4) | Strongly Agree (5) |
| 2. I would make use of this guideline in my professional decisions. | 11% | 11% | 22% | 22% | 33% |
| 3. I would recommend this guideline for use in practice. | 11% | 11% | 22% | 33% | 22% |
| 4. What are the barriers or enablers to the implementation of this guideline report? | <ul style="list-style-type: none"> • Lack of recent data. • documents changing practice; hard to do enablers: good promotion by CCO. | | | | |

Table 4. Summary of written comments by professional consultants and modifications/actions/responses regarding written comments.

| Summary of written comments | Modifications, actions, or responses |
|---|---|
| 1. More the issue of lack of evidence currently available, such that the guideline itself is fine as an academic product, but it would not appear to be particularly helpful in directing the use of specific chemotherapy and allows the clinician to whichever chemotherapy. It will be useful if the guideline can be used to argue for funding for a particular chemotherapy agent. | Funding issue is beyond the scope of this guideline. |
| 2. Although leiomyosarcoma is an uncommon neoplasm, this guideline is based on a very small number of patients. Confidence intervals around response rates and incidence of certain important toxicities are very wide. The authors have over-interpreted the phase II data, and underemphasized the Duffaud abstract that suggests there is no advantage to docetaxel and gemcitabine over gemcitabine alone. Cardiac and lung toxicities have been mentioned in a small number of patients receiving combination therapy in this clinical | Yes, the sample sizes from the eligible studies are small (ranging from 34 to 51 patients in full-texts), but these are the available evidence we can find from the medical literature so far. Just as what we clarified in <u>Section 3</u> , recommendations cannot be made based on published abstracts because some published abstracts may have methodological flaws and would never be fully published. This guideline will be reviewed in three years time to determine if it is still relevant to |

| | |
|--|--|
| <p>setting, whereas the broad experience with gem and docetaxel in many other tumor sites with many-fold more patients did not find these toxicities to occur with close to the frequency reported by the authors. The recommendations regarding cardiac and pulmonary function monitoring are vague and inappropriate based on the data in the evidentiary base.</p> <p>Rather than recommendations to use G-CSF, it would be more appropriate to suggest dose reduction for neutropenia, since this is palliative therapy with limited efficacy and no evidence of survival prolongation. G-CSF would not be covered in Ontario for this indication.</p> | <p>current practice and to ensure that the recommendations are based on the best available evidence. The outcome of the review will be posted on the CCO website. If the French TaxoGem study (an RCT comparing the effect of gemcitabine alone with gemcitabine plus docetaxel) is published soon as a full-text paper and its results and conclusions result in the need to change these guideline recommendations, an update will be initiated as soon as possible.</p> <p>We stated that cardiac and lung toxicities should be monitored for doxorubicin alone, gemcitabine alone, or the combination of gemcitabine plus docetaxel in our recommendations, not only for the combination of gemcitabine plus docetaxel. We now added “neurotoxicity should be monitored” as well.</p> <p>We would recommend the use of G-CSF if the patient has private drug insurance to cover the cost. However, in the absence of private insurance, clinicians may consider dose reduction of chemotherapy and/or the addition of prophylactic oral antibiotics.</p> |
| <p>3. Data for the uses of trabectedin are not discussed at all in this document, and briefly alluded to in the evidentiary base. The Demetri paper does not appear to include uterine leiomyosarcoma; it was almost completely inactive in LMS from other sites (RR<5%), so it would be appropriate to recommend against its use in uterine LMS, in the absence of formal testing in uterine LMS. Both bullets--third bullet in recommendations and key evidence, 1 and 3rd bullet in key evidence sections should be the same: there is NO evidence to support trabectin in this patient population.</p> | <p>The Demetri et al paper included 60 uterine LMS (32 in group one with trabectedin 1.5 mg/m² 24-hour intravenous infusion once every 3 weeks versus 28 in group two with trabectedin 0.58 mg/m² 3-hours every week for 3 weeks of a 4-week cycle), but no subgroup analysis for these patients with uterine LMS. To date, there is insufficient evidence to support the use of trabectedin in the target patients.</p> |

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Sarcoma DSG, the Gynecology Cancer DSG, and the Working Group.

CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, the Sarcoma and Gynecologic Cancer DSG members, and the internal and targeted external reviewers were asked to disclose potential conflicts of interest. The five guideline authors declared they had no conflicts.

One Sarcoma DSG member, CS, declared conflicts and reported receiving \$10,000 or less as honoraria for speaking at annual meetings and \$10,000 for mutational analysis for gastrointestinal stromal tumour from Novartis Oncology; other Sarcoma DSG members had no conflicts of interest. The Gynecologic Cancer DSG members declared they had no conflicts of interest.

The PEBC Assistant Director (HM) and two Research Coordinators (EK and CA) declared that they had no conflicts of interest.

The three RAP members (WE, SH, and MB) declared that they had no conflicts of interest.

For the three targeted external reviewers, none of them had COI.

The COI declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi@mcmaster.ca.

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