program in evidence-based care
a cancer care ontario program

programme de soins fondé sur des preuves
un programme de action cancer ontario

Doxorubicin-based chemotherapy for the palliative treatment of adult patients with locally advanced or metastatic soft tissue sarcoma

Practice Guideline Report #11-1

VHC Bramwell, D Anderson, ML Charette, and members of the Sarcoma Disease Site Group

ORIGINAL GUIDELINE: November 1999
MOST RECENT LITERATURE SEARCH: July 2004

Literature searches conducted since completion of the original guideline have found no new evidence relevant to the recommendations made in the guideline report.

SUMMARY

Guideline Questions

1. Is there an advantage, in terms of response rate or survival, in using doxorubicin-based combination chemotherapy compared with single-agent doxorubicin for palliative treatment of incurable locally advanced or metastatic STS?
2. Is the use of combination chemotherapy associated with increased toxic effects compared with the use of single-agent doxorubicin in this setting?

Target Population

This recommendation applies to adult patients with symptomatic unresectable locally advanced or metastatic soft tissue sarcoma who are candidates for palliative chemotherapy.

Recommendation

- Single-agent doxorubicin is an appropriate first-line chemotherapy option for advanced or metastatic soft tissue sarcoma. Some doxorubicin-based combination chemotherapy regimens, given in conventional doses, produce only marginal increases in response rates, at the expense of increased toxic effects, and with no improvements in overall survival.

Methods

Entries to MEDLINE (through July 2004), EMBASE (through July 2004), CANCERLIT (through to October 2002) and the Cochrane Library (2004, Issue 3) databases and abstracts published in the proceedings of the 1995-2004 annual meetings of the American Society of Clinical Oncology have been searched for evidence relevant to this practice guideline. The most recent literature search was performed in July 2004.

Evidence was selected and reviewed by one member of the Practice Guidelines Initiative's Sarcoma Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Sarcoma Disease Site Group, which comprises medical oncologists, radiation oncologists, surgeons, a pathologist, and community representatives.

External Review by Ontario practitioners is obtained for all practice guidelines through a mailed survey. Final approval of the practice guideline report is obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence

- Eight randomized trials comparing doxorubicin-based combination versus doxorubicin single-agent chemotherapy were reviewed. Response rates and overall survival were evaluated using pooled statistical analysis. The pooled response data in 2281 patients showed a slight trend favouring the combination therapy, although this did not reach statistical significance (odds ratio, 0.79; 95% confidence interval, 0.60 to 1.05; p=0.10). Survival data could only be abstracted from six studies involving 2097 patients, and showed no significant advantage for combination therapy (odds ratio, 0.84; 95% confidence interval, 0.67 to 1.06; p=0.13). Data on adverse effects could not be combined in a meta-analysis; however, nausea, vomiting and myelosuppression were consistently more severe with combination chemotherapy than with single-agent chemotherapy.

Future Research

Future randomized clinical trials should compare new regimens, whose activity has been established in single-arm studies, with single-agent doxorubicin and include quality of life as an outcome measure.

For further information about this practice guideline report, please contact Dr. Shailendra Verma, Chair, Sarcoma Disease Site Group, 503 Smyth Rd, Ottawa, Ontario K1H 1C4; TEL (613) 737-7700, EXT 56792; FAX (613) 247-3511.

The Practice Guidelines Initiative is sponsored by:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.

Visit http://www.cancercare.on.ca/access_PEBC.htm
for all additional Practice Guidelines Initiative reports.

PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.[1] The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, patient representatives and CCO executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

1. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

For the most current versions of the guideline reports and information about the PGI and the Program, please visit the CCO Internet site at:
http://www.cancercare.on.ca/access_PEBC.htm
For more information, contact our office at:
Phone: 905-525-9140, ext. 22055
Fax: 905-522-7681

Copyright

This guideline is copyrighted by Cancer Care Ontario; the guideline and the illustrations herein may not be reproduced without the express written permission of Cancer Care Ontario. Cancer Care Ontario reserves the right at any time, and at its sole discretion, to change or revoke this authorization.

Disclaimer

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the practice guideline is expected to use independent medical judgement in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation nor warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

FULL REPORT

I. QUESTIONS

1. Is there an advantage, in terms of response rate or survival, in using doxorubicin-based combination chemotherapy compared with single-agent doxorubicin for the palliative treatment of patients with incurable locally advanced or metastatic soft tissue sarcoma?
2. Is combination chemotherapy associated with increased toxic effects compared with single-agent doxorubicin in this setting?

II. PATIENT POPULATION

This practice guideline addresses the treatment of patients with locally advanced or metastatic soft tissue sarcoma who are candidates for palliative chemotherapy. Some patients with locally advanced soft tissue sarcomas may be surgical candidates, and multi-disciplinary consultation between a specialized sarcoma surgeon, a radiation oncologist, a medical oncologist, a radiologist and a pathologist should be undertaken to determine the optimal management of these cases. A selected group of patients with metastases confined to the lungs may be suitable for resection with curative intent (1,2), and this option should be considered prior to the use of palliative chemotherapy.

III. CHOICE OF TOPIC AND RATIONALE

Doxorubicin was first identified as an active agent in the treatment of adult soft tissue sarcomas in the 1970s, and response rates in early studies ranged from 9-70% (3). More recently, large randomized multi-centre studies (4-11) have established response rates in the range of 16-27% for single bolus doses of doxorubicin given every three weeks. Subsequently, dacarbazine (DTIC) and ifosfamide (IFOS) were identified as active agents, with single-agent response rates of 18% (12) and 18-36% (13-15), respectively. A large number of other drugs have been evaluated as well, but with minimal or inconsistent activity in patients with soft tissue sarcomas (16).

Various combinations of the active drugs have been evaluated in a number of non-randomized studies (16,17) with documented response rates in the range of 35-60%, but generally at the expense of greater toxicity. Combination chemotherapy regimens not containing doxorubicin have consistently yielded poor results in adult patients with advanced soft tissue sarcoma (5,18,19). Results from large randomized studies (4-11) comparing doxorubicin-based combination chemotherapy regimens with single-agent doxorubicin regimens have been more varied. In some of these trials, response rates have been higher in the combination chemotherapy arms, whereas in others, primary outcomes have not been significantly different between the treatments (6,9,11).

Thus, there is considerable controversy as to whether any added benefit of combination chemotherapy outweighs increased toxic effects and inconvenience to patients, as well as the additional costs to health care systems. This has led to a substantial variation in clinical practice. The Sarcoma Disease Site Group (DSG) felt that a practice guideline, based on an unbiased, systematic review of the evidence, was warranted.

IV. METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care, using the methods of the Practice Guidelines Development Cycle (20). Evidence was selected and reviewed by one member of the PGI's Sarcoma DSG and methodologists.

The practice guideline report is a convenient and up-to-date source of the best available evidence on doxorubicin-based chemotherapy for the palliative treatment of adult patients with

locally advanced or metastatic soft tissue sarcoma, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. The body of evidence in this report is primarily composed of mature randomized controlled trial data; therefore recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners is obtained for all practice guideline reports through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the recommendations should serve as a practice guideline. Final approval of the practice guideline report is obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature, and where appropriate, integration of this literature with the original guideline information.

Literature Search Strategy

MEDLINE (Ovid) (from 1966) and CANCERLIT (Ovid) (from 1975) were searched in December 1997. "Doxorubicin" (MESH term and text word) was combined with "Combin" (truncated text word), and "Sarcoma" (MESH term and text word) and these terms were then combined with search terms for the following study designs: practice guidelines, systematic reviews or meta-analysis, and randomized controlled trials. This search was updated in April and December of 1998, and again in June of 1999. EMBASE was also searched from 1979 to 1995 using the truncated keywords, "random" and "sarcoma". Citation lists and personal files were scanned for additional studies. The Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/), the American Society of Clinical Oncology (ASCO) Annual Meeting Proceedings (1995-1999), and the Cochrane Library (Issue 2, 1999) were also searched for additional reports of completed or ongoing trials. No further attempt was made to find reports of unpublished randomized controlled trials. Relevant articles and abstracts were selected and assessed by two reviewers (VB, DA) and the reference lists from these sources were searched for additional trials.

Update

The original literature search has been updated using MEDLINE (through July 2004) EMBASE (1980 through July 2004), CANCERLIT (through October 2002), the Cochrane Library (Issue 3, 2004) and the 2000-2004 proceedings of the annual meeting of ASCO.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. Randomized controlled trials comparing single-agent doxorubicin with a doxorubicin-based combination chemotherapy regimen.
2. Involved adult patients with locally advanced or metastatic soft tissue sarcoma in the palliative setting.
3. Potential studies had to measure response rate, overall survival and toxic effects or quality of life.
4. Abstracts of trials were also considered.

Exclusion Criteria

1. Phase I and II studies were not considered for inclusion in this report because of the availability of randomized controlled trials.
2. Letters and editorials were not considered.
3. Papers published in a language other than English were not considered.

Synthesizing the Evidence

The intent was to combine (i.e., pool) data from all eligible trials, in order to calculate overall estimates of treatment efficacy and harm. Pooled results were expressed as an odds ratio (OR), which is the odds of an event occurring in the experimental group over the odds of an event occurring in the control group, with a 95% confidence interval (CI). Target events were consistently unfavourable (e.g., death at two years, no complete or partial response, etc.), so that estimates greater than 1.0 favoured the control group (single-agent therapy) and estimates less than 1.0 favoured experimental group (combination therapy). The more conservative random effects model was used in the meta-analyses to allow for the differences in trial design and quality (21). A statistical Q-test was used to measure the quantitative heterogeneity among study results. Calculations for the meta-analysis were performed on a Pentium PC using the software program, Metaanalyst$^{0.988}$, created by Dr. Joseph Lau (Boston, MA).

V. RESULTS

Literature Search Results

There were eight randomized controlled trials identified which met the eligibility criteria (4-11), comparing doxorubicin combination chemotherapy with single-agent doxorubicin. Trial characteristics, including the chemotherapy regimens, are shown in Table 1. Outcome measures across all eight trials included response rates, median survival and various measures of toxicity, and these are shown in Tables 2 and 3. Response duration and time to progression were not reported consistently across studies and could not be analysed further. There were no practice guidelines or systematic reviews identified in the literature search.

Update

No new trials were identified in any of the updated searches.

Description of Studies

There were nine single-agent doxorubicin arms (1,086 total patients entered) in the eight studies. One study evaluated doxorubicin given in two different schedules. Each study included an arm in which high-dose single-agent doxorubicin was given every three weeks. In three studies the dose was 60 mg/m^2 (4,6,7), in three studies 70 mg/m^2 (5,8,9), and 75 mg/m^2 (11) and 80 mg/m^2 (10) were given in one study each. In one study (8), there was an additional arm in which doxorubicin (20 mg/m^2 daily x 3) was administered as a loading dose followed by 15 mg/m^2 weekly.

There were ten doxorubicin-based combination chemotherapy regimens given in eight studies (1,195 total patients entered). The dose of doxorubicin in combination with other agents was 40 mg/m^2 in one study (10), 50 mg/m^2 in two studies (5,11), 60 mg/m^2 in five studies (4,6-8,10), and 70 mg/m^2 in one study (9); in each case treatment was repeated every three weeks. The doxorubicin-based combination chemotherapies included doxorubicin with either vindesine (9), streptozotocin (4), or cyclophosphamide (7); doxorubicin with ifosfamide in two studies (10,11); doxorubicin with DTIC in two studies (6,8); doxorubicin with mitomycin-C and cisplatin in one study (10); doxorubicin with vincristine and cyclophosphamide in one study (5); and doxorubicin with vincristine, cyclophosphamide and DTIC in one study (11).

Although a few patients who had received previous chemotherapy (Table 1) were included in the earlier studies (4-6) most patients were chemotherapy-naive when they entered

these studies. Similarly, the majority had adult soft tissue sarcoma, although a few bone sarcomas and mesotheliomas were included in three studies (4,5,10). All the trials excluded some patients entered on study who were subsequently found to be ineligible and a variable number of patients were found not to be evaluable for response (Table 1).

Table 2 outlines response rates and durations of median survival, which were consistently reported across all studies. Response rates for single-agent doxorubicin ranged between 16% and 27%. Response rates for combination chemotherapy ranged from a low of 14% for doxorubicin and streptozotocin (4) to 34% for doxorubicin and ifosfamide (10). Response rates were significantly better for the combination chemotherapy regimens in only two trials. In one study (8) the combination of doxorubicin and DTIC was superior to doxorubicin ($p=0.03$), given by two different schedules, and in the second study (10) the combination of doxorubicin and ifosfamide was superior to single-agent doxorubicin ($p=0.03$). In one study (5) response rate was significantly better on doxorubicin compared with the combination of doxorubicin/vincristine/cyclophosphamide ($p=0.03$). None of the studies showed any significant differences in median survival time between single-agent doxorubicin and combination chemotherapy.

Table 1. Randomized controlled trials of doxorubicin combination chemotherapy in adult patients with incurable locally advanced or metastatic soft tissue sarcoma.

Study	Tumour type	Chemotherapy	Regimens*	# Rand. Pts. (evaluable)
Chang & Wiernik, 1976 (4) NCI (US)	Adult STS (4 bone sarcomas) 4 prior chemo	DOX	60 mg/m^2 IV bolus	18 (17)
		DOX STREPT	60 mg/m^2 IV bolus 500 mg/m^2 IV bolus d1-5	15 (14)
Schoenfeld et al, 1982 (5) † ECOG	Adult STS (18 bone sarcomas, 9 mesotheliomas) 3 prior chemo	DOX	70 mg/m^2 IV bolus	71 (66)
		DOX VCR CYCLO	50 mg/m^2 IV bolus 1.4 mg/m^2 IV bolus 750 mg/m^2 IV bolus	80 (70)
Omura et al, 1983 (6) GOG	Uterine sarcomas 31 prior chemo	DOX	60 mg/m^2 IV bolus	155 (120)
		DOX DTIC	60 mg/m^2 IV bolus 250 mg/m^2 IV bolus d1-5	160 (106)
Muss et al, 1985 (7) GOG	Uterine sarcomas	DOX	60 mg/m^2 IV bolus	66 (50)
		DOX CYCLO	60 mg/m^2 IV bolus 500 mg/m^2 IV bolus	66 (54)
Borden et al, 1987 (8) ECOG	Adult STS	DOX	70 mg/m^2 IV bolus	123 (94)
		DOX	20 mg/m^2 d1,2,3 IV bolus, then 15 mg/m^2/wk	119 (88)
		DOX DTIC	60 mg/m^2 IV bolus 250 mg/m^2 IV bolus d1-5	119 (92)
Borden et al, 1990 (9) ECOG	Adult STS	DOX	70 mg/m^2 IV bolus	176 (151)
		DOX VND	70 mg/m^2 IV bolus 3 mg/m^2 IV bolus	171 (147)
Edmonson et al, 1993 (10) ECOG	Adult STS (4 bone sarcomas)	DOX	80 mg/m^2 IV bolus	95 (90)
		DOX IFOS	60 mg/m^2 IV bolus 3.75 g/m^2 IV 4 hrs x 2 days	94 (88)
		DOX MITC DDP	40 mg/m^2 IV bolus 8 mg/m^2 IV bolus 60 mg/m^2 IV bolus	90 (84)
Santoro et al, 1995 (11) EORTC	Adult STS	DOX	75 mg/m^2 IV bolus	263 (240)
		DOX VCR CYCLO DTIC	50 mg/m^2 IV bolus 1.5 mg/m^2 IV bolus 500 mg/m^2 IV bolus 750 mg/m^2 IV 30 mins	142 (134)
		DOX IFOS	50 mg/m^2 IV bolus 5 g/m^2 CIV 24 hrs	258 (231)

NOTE: CYCLO = cyclophosphamide; d = day; DDP = cisplatin; DOX = doxorubicin (Adriamycin); DTIC = dacarbazine; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; GOG = Gynecologic Oncology Group; hrs = hours; IFOS = ifosfamide; mins = minutes; MITC = mitomycin; NCI = National Cancer Institute; STREPT = streptozotocin; STS = soft tissue sarcoma; VCR = vincristine; VND = vindesine; wk = weeks

* all doses given every three weeks, unless otherwise stated. † third arm: vincristine, Actinomycin D, cyclophosphamide.

Table 2. Response rates and medial survival times reported in randomized trials of doxorubicin chemotherapy.

Study	Treatment	# Evaluable patients	# Responders (%)	Median survival (months)
Chang & Wiernick, 1976 (4)	DOX	17	4 (24)	10.2
	DOX/STREPT	14	2 (14) p=NS	10.6
Schoenfeld et al, 1982 (5)	DOX	66	18 (27)	8.5
	DOX/VCR/CYCLO	70	13 (19) p=0.03*	7.8
Omura et al, 1983 (6)	DOX	120	13/80 (16)	7.7
	DOX/DTIC	106	16/66 (24) p=NS	7.3
Muss et al, 1985 (7)	DOX	50	5/26 (19)	11.6
	DOX/CYCLO	54	5/26 (19) p=NS	10.9
Borden et al, 1987 (8)	DOX q 3 wk	94	17 (18)	8.0
	DOX loading → weekly	88	15 (17)	8.4
	DOX/DTIC	92	28 (30) p=0.03†	8.0
Borden et al, 1990 (9)	DOX	151	26 (17)	9.4
	DOX/VND	147	26 (18) p=NS	9.9
Edmonson et al, 1993 (10)	DOX	90	18 (20)	8.4
	DOX/IFOS	88	30 (34)	11.5
	DOX/MITC/DDP	84	27 (32) p=0.03†	9.4
Santoro et al, 1995 (11)	DOX	240	56 (23)	12.0
	DOX/VCR/CYCLO/DTIC	134	38 (28)	11.8
	DOX/IFOS	231	65 (28) p=NS	12.7

NOTE: CYCLO = cyclophosphamide; DDP = cisplatin; DOX = doxorubicin (Adriamycin); DTIC = dacarbazine; IFOS = ifosfamide; MITC = mitomycin; NS = not significant; STREPT = streptozotocin; VCR = vincristine; VND = vindesine.

* Single-agent doxorubicin better than combination chemotherapy.

† Doxorubicin combination chemotherapy better than single-agent doxorubicin.

Assessment of Trial Quality

Studies included in this systematic overview were published between 1976 and 1995. In general, later reports included more details about methodology, particularly statistical analysis. Five studies described a satisfactory (central office) method of randomization (5,8-11), and four studies (6,8,9,11) included an outline of statistical methodology in the Patient/Materials and Methods section. However, in only two papers (9,11) were accrual goals set and met. The studies conducted by Chang et al (4) and Muss et al (7) were of inadequate size to properly evaluate differences in response rate or survival. Although response criteria were described or referenced in all except one study (5) it is generally accepted that the quality of evaluation of response has improved over the past 20 years because of better imaging techniques and attention to quality-control procedures. Thus, the results reported in later studies may be more reliable. Two papers (5,6) provided very limited data on toxic effects, and only two papers provided detailed tabular reports of toxic effects seen in multiple systems (9,11). In five studies (6-8,10) central pathology review was performed in a majority of tumours. Some analysis of the delivered dose of relevant drugs was performed in four studies (7,8,10,11).

Overall, it was not felt that there were a sufficient number of papers in which the quality exceeded the remainder, to justify a sensitivity analysis based on quality. However, a sensitivity analysis was performed on the four trials (6,8,10,11) that included a combination of doxorubicin with at least one of the other known active agents for soft tissue sarcoma (i.e. ifosfamide and DTIC) in their regimens.

Meta-analysis Results

Data were combined for objective tumour response and overall survival. A statistical Q-test showed no significant numerical heterogeneity across studies for these two outcomes. The Q-test values were 9.45 for objective tumour response and 3.42 for overall survival. Adverse effects data were not combined, as the outcomes and measures varied greatly among studies.

Objective Tumour Response

Objective tumour response (complete and partial) data were available and consistently reported in all eight trials, providing eight comparisons with a total of 2281 patients. The trials ranged in size from 663 randomized patients (11) to 33 randomized patients (4). Results of pooling response data (Figure 1) showed a slight trend favouring the combination therapy, though this did not reach statistical significance (OR, 0.79; 95% CI, 0.60 to 1.05; p=0.10). However, when the data pooled were restricted to the four trials involving combination regimens of known active agents (6,8,10,11), this trend disappeared (OR, 0.71; 95% CI, 0.45 to 1.13; p=0.15).

Overall Survival

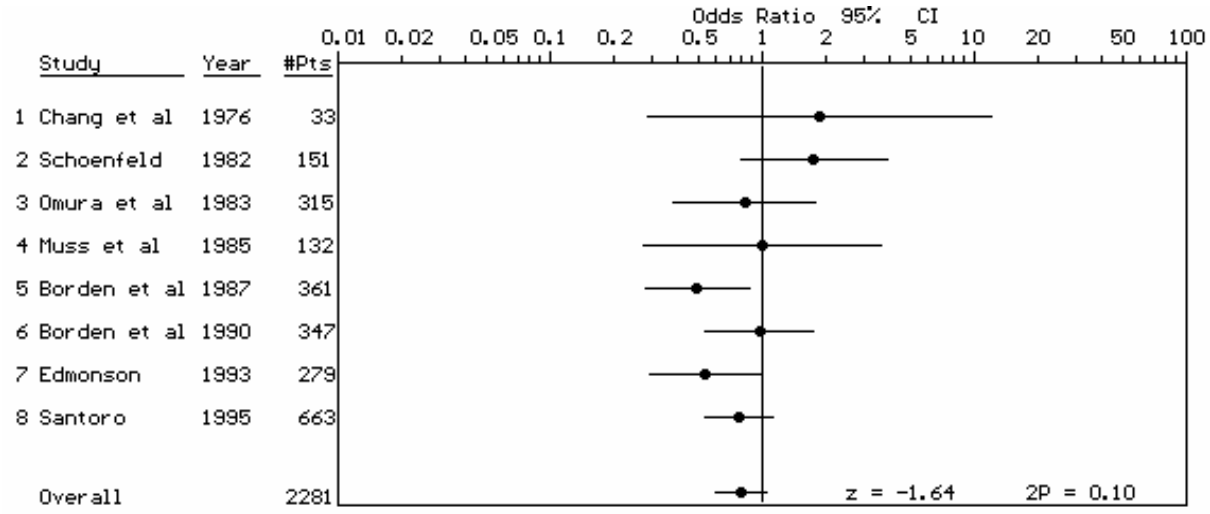
Survival data were extracted directly from probability graphs for six of the eight trials, for a total of 2097 patients. In two trials, survival data either were not reported (4), or could not be extracted (5). Trial size ranged from 663 randomized patients (11) to 132 randomized patients (7). Results of pooling this outcome measure across six studies (Figure 2) were not statistically significant (OR, 0.84; 95% CI, 0.67 to 1.06; p=0.13), and the results did not significantly change when the data were restricted to the four trials using combinations of known active agents (OR, 0.90; 95% CI, 0.69 to 1.20; p=0.48).

Epirubicin

Consideration was given to broadening the guideline to include any randomized studies of single agent anthracycline versus the same anthracycline in combination with other agents. Epirubicin has been evaluated as a single agent in two European Organization for Research and Treatment of Cancer (EORTC) randomized trials (22,23), as well as in a number of single-

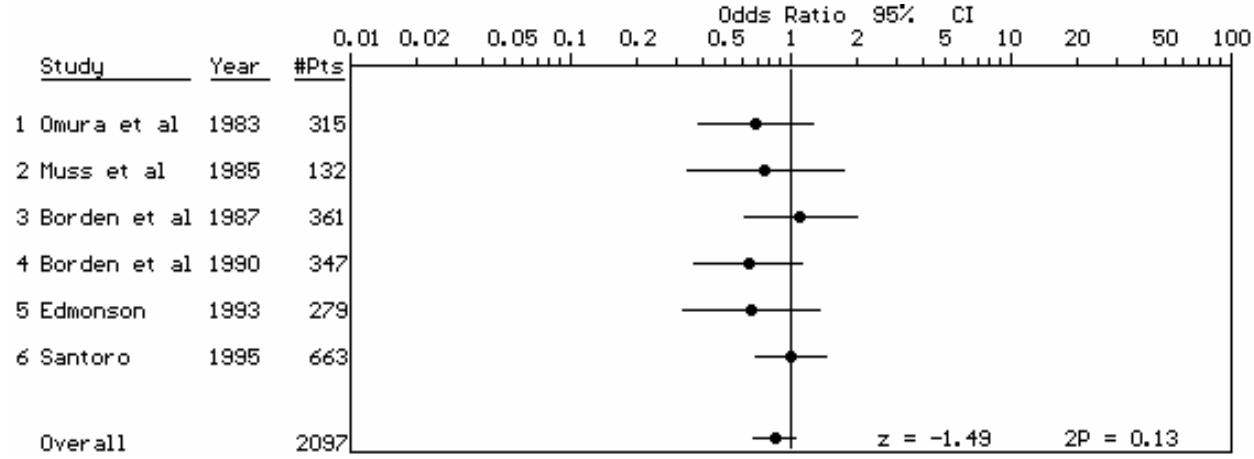
arm combination chemotherapy studies. In the second EORTC study (23), high-dose epirubicin 150 mg/m^2 every 3 weeks given by two different schedules produced similar response rates (14-15%) to standard-dose doxorubicin 75 mg/m^2 every 3 weeks (14%), with no difference in overall survival (p=0.89). In one randomized study from Serbia (24), 50 patients receiving epirubicin 60 mg/m^2/24 hr on days one to three (Group A) were compared with 56 patients given the same dose of epirubicin + cisplatin 30 mg/m^2/24 hr on days two to five (Group B). The response rate was higher for Group B (54% vs. 29%, $p < 0.025$) and so was overall survival (p=0.001). However, median survival times were approximately 10 months versus 8 months, in the same range as the median survival times in studies shown in Table 2. Adding this study to the meta-analyses did not significantly alter the outcomes for response rate (OR, 0.74; 95% CI, 0.55 to 1.00; p=0.051) (Figure 3) or survival (OR, 0.78; 95% CI, 0.60 to 1.03; p=0.078) (Figure 4). In view of the very limited data on epirubicin, the conclusions and practice guideline are based on the doxorubicin studies.

Figure 1. Meta analysis results for objective tumour response (complete and partial).



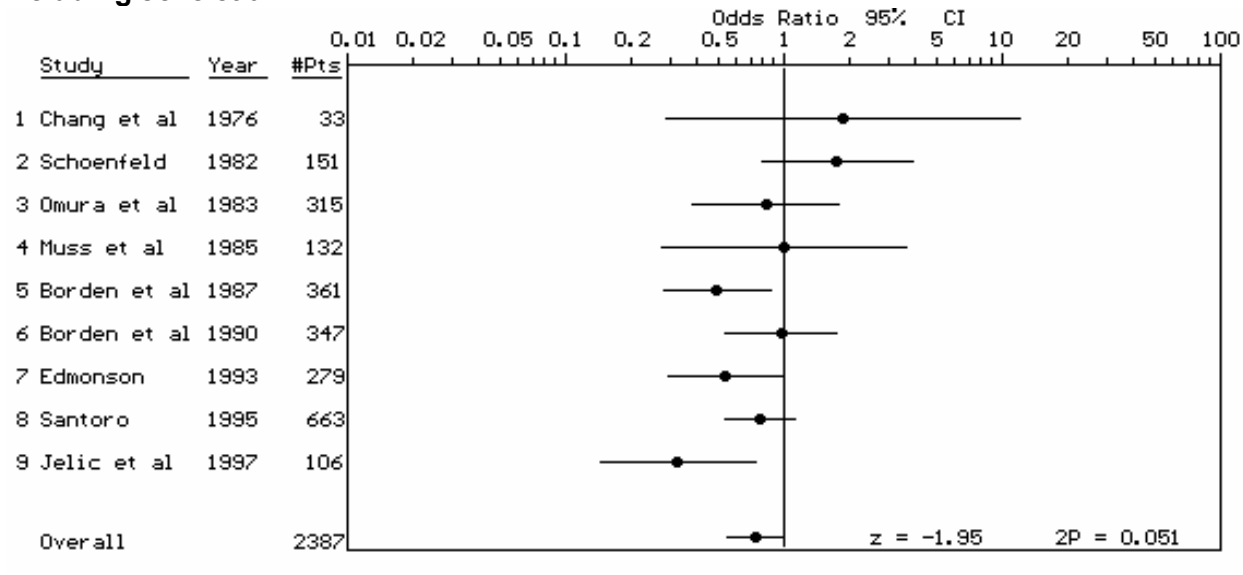
Favours combination therapy ≈ ≡ Favours single-agent therapy
Overall odds ratio = 0.79 (95% CI, 0.60 to 1.05; p=0.10)

Figure 2. Meta analysis results for survival (at 2 years).



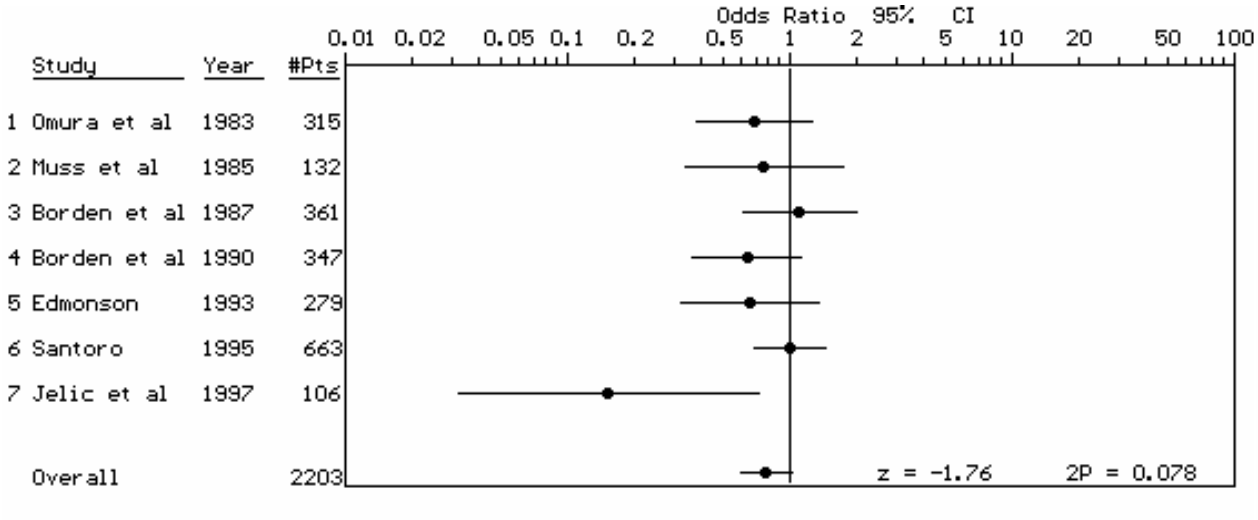
Favours combination therapy ≈ ≡ Favours single-agent therapy
Overall odds ratio = 0.84 (95% CI, 0.67 to 1.06; p=0.13)

Figure 3. Meta analysis results for objective tumour response (complete and partial) including Jelic et al.



Favours combination therapy ≈ ≡ Favours single-agent therapy
Overall odds ratio = 0.74 (95% CI, 0.55 to 1.00; p=0.051)

Figure. 4 Meta analysis results for survival at two years including Jelic et al.



Favours combination therapy ≈ ≡ Favours single-agent therapy
Overall odds ratio = 0.78 (95% CI, 0.60 to 1.03; p=0.078)

Table 3. Toxic effects reported in randomized trials of doxorubicin chemotherapy.

Study	Treatment	Toxic effects		
		Nausea & Vomiting	WBC Count	Platelet Count
Chang & Wiernick, 1976 (4)	DOX	59% mild/mod	WBC <2000 9%	PLATS <100,000 3%
	DOX + STREPT	100% mod/severe	30% (p<0.01)	13% (p<0.03)
Schoenfeld et al, 1982 (5)	DOX	42% mod/severe	Hematologic 17% severe	
	DOX/VCR/CYCLO	60% mod/severe (p=0.09)	30% severe (p=0.07)	
Omura et al, 1983 (6)	DOX	Grade 3/4 2.2%	Grade 3/4 16%	Grade 3/4 4%
	DOX/DTIC	8.5%	35%	13%
Muss et al, 1985 (7)	DOX	0% severe	WBC <2000 10%	PLATS<50,000 0%
	DOX/CYCLO	6% severe	35%	0%
Borden et al, 1987 (8)	DOX q 3 wk	11% severe	Hematologic 28% severe	
	DOX loading q/wk	6% severe	13% severe	
	DOX/DTIC	29% severe (p=0.00003)	29% severe (p=0.87)	
Borden et al, 1990 (9)	DOX	6% severe	Hematologic 36% severe	
	DOX/VND	3% severe	50% severe	
Edmonson et al, 1993 (10)	DOX	7% severe	Hematologic 53%	
	DOX/IFOS	18% severe	80%	
	DOX/MITC/DDP	17% severe	55% (p=0.01)	
Santoro et al, 1995 (11)	DOX	Grade 3/4 17%	Grade 4 13%	Grade 3/4 4%
	DOX/VCR/CYCLO/DTIC	40%	15%	10%
	DOX/IFOS	NR	32% (p<0.001)	6%

NOTE: CYCLO=cyclophosphamide; DDP=cisplatin; DOX=doxorubicin (Adriamycin); DTIC=dacarbazine; IFOS=ifosfamide; MITC=mitomycin; NR = not reported; STREPT=streptozotocin; VCR=vincristine; VND=vindesine; WBC = white blood cell.

Adverse Effects

Reporting of adverse effects was quite variable among the eight eligible trials. Most of the studies reported nausea/vomiting and hematological toxic effects. As all these studies were performed before the widespread use of $5HT_3$-antagonists, nausea and vomiting were reported frequently. As can be seen from Table 3, with the exception of the study reported by Borden and colleagues (9), nausea and vomiting were always greater for combination regimens, often significantly so. Similarly, hematologic toxic effects were reported in different ways among studies. Sometimes leucopenia and thrombocytopenia were reported separately, sometimes in combination. In many of these studies, nadir blood counts were not necessarily performed and there may be under-reporting of hematological toxicity. Again, it is evident from Table 3 that the hematologic toxicity of combination chemotherapy was always higher than single-agent doxorubicin. Neutropenic fever was not reported consistently; neither were other toxic effects, such as mucositis. Although the more recent studies (8-11) did report toxic deaths, these were uncommon across all the studies. Reporting of cardiotoxicity was highly variable and it was impossible to determine whether this was worse for single-agent or combination regimens; ultimately, it depended on the individual dose of doxorubicin received by each patient. Quality of life was not addressed in any of the studies included in this report.

VI. INTERPRETIVE SUMMARY

Response rates for combination chemotherapy were significantly better than for single-agent doxorubicin in only two of the eight randomized trials. Pooling of response data showed a slight trend favouring combination chemotherapy (OR, 0.79; 95% CI, 0.60 to 1.05), but this did not achieve statistical significance (p=0.10). Similarly, combining survival data did not show a significant difference between treatment groups (OR, 0.84; 95% CI, 0.67 to 1.06; p=0.13). Although reporting of adverse effects was limited and inconsistent among trials (making pooling of data for this outcome problematic), side effects such as nausea/vomiting and hematologic toxic effects were consistently reported as being worse with combination chemotherapy across the eight eligible studies.

A number of authors have suggested that response to chemotherapy may vary with histological subtype, although there are discrepancies between studies in identifying the most and least responsive histologies. Potential flaws of these studies include insufficient patient numbers for reliable statistical analysis and variability in pathological interpretation. The most extensive database, which has been subjected to central histopathological review, has been established by the EORTC Soft Tissue and Bone Sarcoma Group. Van Glabbeke et al (25) reported on 2,185 patients with advanced STS treated in seven clinical trials investigating the use of anthracycline-containing regimens as first-line chemotherapy. Univariate analysis showed increased survival times for patients with liposarcoma and synovial sarcoma, decreased survival times for patients with malignant fibrous histiocytoma and a higher response rate for patients with liposarcoma ($p<0.05$ for all log-rank and X^2 tests). However, by multivariate analysis, the only significant influence of pathological subtype documented was that a diagnosis of liposarcoma was a favourable prognostic factor for response rate (p=0.0065).

The main limitation of the present review is the fact that a number of different doxorubicin-based combination chemotherapy regimens have been compared with doxorubicin. Four of the eight studies compared combinations which included drugs considered to have limited activity as single-agent regimens in advanced soft tissue sarcoma (i.e. vincristine, vindesine, cyclophosphamide, streptozotocin, mitomycin-C, cisplatin). But even the four studies which used the known active agents in combination with doxorubicin (i.e. ifosfamide and DTIC) produced mixed results. Thus, the response rate for doxorubicin and DTIC was better than that for doxorubicin in one study (8) and similar in another study (6). Also, for doxorubicin and ifosfamide, the response rate was better than for doxorubicin alone in the study reported by Edmonson and colleagues (10), but similar in the EORTC study reported by Santoro and

colleagues (11). A meta-analysis of these four trials did not demonstrate a significant difference. The three-drug combination of doxorubicin, DTIC and ifosfamide (MAID) has never been directly compared with doxorubicin alone. However, in a recent randomized study, a superior response rate was shown for MAID compared with the combination of doxorubicin and DTIC (32% vs. 17%, $p<0.002$) but with increased myelosuppression and no improvement in overall survival (26). Since the publication of these studies, no new active drugs have been identified in soft tissue sarcoma.

In virtually all of the reviewed studies, the toxic effects of combination chemotherapy (particularly nausea and vomiting, myelosuppression) exceeded that of single-agent doxorubicin. It can be argued that modern anti-emetics and growth factor support might reduce or eliminate these differences, but in the setting of palliative chemotherapy, the costs of such strategies (particularly with granulocyte colony-stimulating factor (G-CSF)) must be weighed against the expected benefits.

In the reviewed studies, 633 of 1086 (58%) patients receiving doxorubicin were given a dose of 70-75 mg/m^2 every three weeks. Toxicity data from these studies were too sparse to provide an evidence-based recommendation regarding dose. However, the EORTC has extensive experience of the safety and efficacy of doxorubicin 75 mg/m^2 every three weeks (11,22,27), and this dose schedule is commonly used by sarcoma specialists throughout North America and Canada. Thus, for the palliative treatment of symptomatic locally advanced or metastatic soft tissue sarcoma, an appropriate starting dose schedule of doxorubicin is 75 mg/m^2 intravenously every three weeks.

In summary, combinations of the known active drugs used at conventional doses can produce marginal increases in response rate in advanced metastatic soft tissue sarcoma, at the expense of increased adverse effects, but do not significantly increase survival rates. Thus the results of this analysis favour the use of single-agent doxorubicin for palliative treatment of advanced/metastatic soft tissue sarcoma.

VII. ONGOING TRIALS

The National Cancer Institute's clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) was searched for Phase III study protocols involving doxorubicin-based chemotherapy treatment. Tumour type was not specified in the search strategy.

Protocol ID(s)	Title and details of trial
EORTC-62012	Phase III Randomized Study of Doxorubicin With Versus Without Ifosfamide in Patients With Locally Advanced or Metastatic Soft Tissue Sarcoma. Outcomes: overall and progression-free survival, response, toxicity. Projected accrual: 450 patients within 4 years. Status: active. Summary last modified: May 23, 2003. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=302584&version=HealthProfessional&protocolsearchid=1050491.

VIII. DISEASE SITE GROUP CONSENSUS PROCESS

Members of the Sarcoma Disease Site Group (DSG) focussed their discussion on the evidence for doxorubicin-based combination chemotherapy in advanced soft tissue sarcoma. It was discussed whether to include the MAID regimen in this guideline report, but since this regimen has not been tested in a randomized controlled trial comparing it with single-agent doxorubicin, it was excluded. It is given brief mention above in Section VI.

There was some discussion on the quality and consistency of the trials included in this report. While all the studies included were randomized controlled trials, there was some variation as to the treatment regimens and dosages used, and the type and stage of tumour being treated. The studies also varied in the number of patients randomized, and the quality and level of detail reported in their methods and results. The DSG felt these differences should be noted in the guideline. The group decided to add a sensitivity analysis to the meta-analysis, by combining data from the four studies using active agents in combination with doxorubicin (i.e. IFOS and DTIC) in order to see if this affected the results for response and survival outcomes.

While the group felt that more could be written on the increased adverse effects of combination chemotherapy as compared to single-agent regimens, they also recognized the difficulties in pooling adverse effects data that has been measured using different toxicity scales. The group decided not to combine adverse effects (toxicity) data, as this would be inappropriate.

There was also some discussion surrounding the lack of quality of life data and the use of response as an endpoint. Sarcoma studies are performed slowly, and many of the trials included in the report were completed before quality of life assessment tools were developed. Thus, response rate has been accepted as a surrogate for quality of life in patients in whom a response may relieve symptoms. The members of the DSG were in agreement that quality of life is an important end point and decided to add a point to the recommendation itself, stating that quality of life measures should be included as primary end points in future randomized clinical trials.

IX. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

This section describes the external review activities undertaken for the original guideline report.

Draft Recommendations

Based on the evidence described in the original report above, the Sarcoma DSG drafted the following recommendation:

Target Population

These recommendations address the treatment of adult patients with locally advanced or metastatic soft tissue sarcoma who are candidates for palliative chemotherapy.

Draft Recommendations

- Single-agent doxorubicin (60-80 mg/m^2 intravenously, every three weeks) is an appropriate first-line chemotherapy option for the palliative treatment of advanced or metastatic soft tissue sarcoma. Some combination chemotherapy regimens, given in conventional doses, produce only marginal increases in response rates, at the expense of increased toxic effects, and with no improvements in overall survival.
- Future randomized clinical trials should compare active new regimens, identified in single-arm studies, with single-agent doxorubicin, and include quality of life as an end point.
- Multi disciplinary consultation with a specialized sarcoma surgeon, a radiation oncologist and a medical oncologist is recommended to determine the optimal management of locally advanced soft tissue sarcomas.
- A selected group of patients with metastases confined to the lungs may be suitable for resection of metastases with curative intent, and this option should be considered prior to the use of palliative chemotherapy.

Practitioner Feedback

Based on the evidence contained in the original report and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 53 practitioners in Ontario (29 medical oncologists, 11 radiation oncologists, eight surgeons, four gynecologists and one pharmacist). The survey consisted of items evaluating the methods, results and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey were reviewed by the Sarcoma DSG.

Results

Key results of the practitioner feedback survey of the original draft guideline report are summarized in Table 4. Thirty-four (64%) surveys were returned. Twenty-five (74%) respondents indicated that the evidence-based recommendation was relevant to their clinical practice and they completed the survey.

Summary of Main Findings

Seventeen (50%) respondents provided written comments. The main points were:

1. A number of practitioners pointed out that the third and fourth bullets of the EBR were not evidence-based recommendations.
2. A request was made that there be some acknowledgement of trials using epirubicin alone or in combination in this setting.
3. A query was made regarding the correlation of response to chemotherapy with histological subtype of sarcoma.
4. One practitioner stated a belief that a regimen with a 30% response rate would provide a significant palliative benefit to more patients than a regimen that produced an 18% response rate.
5. A practitioner suggested that uterine sarcomas may be different from other soft tissue sarcomas.
6. Some practitioners suggested reviewing data on other agents or combinations, or producing a guideline on the general management of soft tissue sarcoma.
7. The therapeutic ratio for doxorubicin is relatively narrow. A starting dose of 60 mg/m^2 is now considered low, and doses as high as 80-90 mg/m^2 substantially increase toxicity. Most sarcoma specialists consider doses of doxorubicin 70-75 mg/m^2 intravenously every three weeks to be optimal for palliative therapy.

Table 4. Practitioner responses to seven items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a clinical practice guideline, as stated in the "*Choice of Topic*" section of the report, is clear.	24 (96)	1 (4)	0 (0)
There is a need for a clinical practice guideline on this topic.	22 (88)	2 (8)	1 (4)
The literature search is relevant and complete.	25 (100)	0 (0)	0 (0)
The results of the trials described in the report are interpreted according to my understanding of the data.	22 (88)	2 (8)	1 (4)
I agree with the draft recommendations as stated.	19 (76)	4 (16)	2 (8)
This report should be approved as a practice guideline.	18 (72)	5 (20)	2 (8)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	**Very likely or likely**	**Unsure**	**Not at all likely or unlikely**
	17 (68)	5 (20)	3 (12)

Modifications/Actions

1. Although the third and fourth bullets of the EBR are not evidence-based recommendations, they are important points. Accordingly, they have been moved into Section II of this guideline report, which describes the patient population. The point regarding multi-disciplinary consultation now includes a pathologist and a radiologist.
2. Trials using epirubicin are described in Section V, subsection Meta-analysis Results.
3. With regard to the correlation of response to chemotherapy with histological subtype of sarcoma, a paragraph has been added to the Interpretive Summary section of this document.
4. Regarding the statement about palliative benefit, the members of the Sarcoma DSG felt that there was no evidence for this statement, as palliative benefit depends not only on response rate, but also on toxicity. Formal evaluation of quality of life was not performed in any of the studies included in this EBR. Thus, no changes have been made to correspond with this suggestion.
5. Two of the eight studies quoted in this EBR, which accrued 41% of the total patients, evaluated uterine sarcomas. The results were very similar to the other six studies, thus no changes were made.
6. Reviewing data on other agents or combinations, or producing a guideline on the general management of soft tissue sarcoma were not the focus of this particular guideline, but may be considered in future practice guidelines.
7. This comment was felt to be valid. A paragraph on dose scheduling was added to the Interpretive Summary, and the dose range of 60-80 mg/m^2 intravenously was removed from the Practice Guideline.

Approved Practice Guideline Recommendations

This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. They have been approved by the Sarcoma DSG and the Practice Guidelines Coordinating Committee.

X. POLICY IMPLICATIONS

Single-agent doxorubicin can be given on an outpatient basis at lesser cost in contrast with some combination chemotherapy regimens, particularly those involving ifosfamide, which require inpatient delivery. Reduced drug acquisition costs, and a possible reduced need for supportive care drugs may be added economic benefits of single-agent doxorubicin. However, the use of other active agents, such as ifosfamide, as second-line therapy in selected fit patients failing or relapsing after response to doxorubicin, may partially off-set these cost savings.

XI. PRACTICE GUIDELINE

This practice guideline reflects the most current information reviewed by the Sarcoma DSG.

Target Population

This recommendation applies to adult patients with symptomatic unresectable locally advanced or metastatic soft tissue sarcoma who are candidates for palliative chemotherapy.

Recommendations

- Single-agent doxorubicin is an appropriate first-line chemotherapy option for advanced or metastatic soft tissue sarcoma. Some doxorubicin-based combination chemotherapy regimens, given in conventional doses, produce only marginal increases in response rates, at the expense of increased toxic effects, and with no improvements in overall survival.

Future Research

Future randomized clinical trials should compare new regimens, whose activity has been established in single-arm studies, with single-agent doxorubicin, and include quality of life as an outcome measure.

XII. JOURNAL REFERENCE

Bramwell VHC, Anderson D, Charette ML. Doxorubicin-based chemotherapy for the palliative treatment of adult patients with locally advanced or metastatic soft-tissue sarcoma: a meta-analysis and clinical practice guideline. *Sarcoma* 2000;4(3):103-12.

XIII. ACKNOWLEDGMENTS

The Sarcoma Disease Site Group would like to thank Dr. Vivien Bramwell and Dale Anderson for taking the lead in drafting and revising this practice guideline report.

The Sarcoma Disease Site Group would like to thank Dr. Vivien Bramwell, Manya Charette, and Tricia Kirchner for taking the lead in updating this practice guideline report.

For a complete list of the Sarcoma Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit the CCO Web site at: http://www.cancercare.on.ca/access_PEBC.htm.

REFERENCES

1. Frost, DB. Pulmonary metastasectomy for soft tissue sarcomas: Is it justified? *J Surg Oncol* 1995;59:110-5.
2. van Geel AN, Pastorino U, Jauch KW, Judson IR, van Coevorden F, Buesa JM, et al. Surgical treatment of lung metastases: The European Organization for Research and Treatment of Cancer - Soft Tissue and Bone Sarcoma Group study of 255 patients. *Cancer* 1996;77:675-82.
3. Pinedo HM, Kenis Y. Chemotherapy of advanced soft-tissue sarcomas in adults. *Cancer Treat Rev* 1977;4:67-86.
4. Chang P, Wiernik PH. Combination chemotherapy with adriamycin and streptozotocin. I. Clinical results in patients with advanced sarcoma. *Clin Pharmacol Ther* 1976;20:605-10.
5. Schoenfeld DA, Rosenbaum C, Horton J, Wolter JM, Falkson G, DeConti RC. A comparison of adriamycin versus vincristine and adriamycin, and cyclophosphamide versus vincristine, actinomycin-d and cyclophosphamide for advanced sarcoma. *Cancer* 1982;50:2757-62.
6. Omura GA, Major FJ, Blessing JA, Sedlacek TV, Thigpen JT, Creasman WT, et al. A randomized study of adriamycin with and without dimethyl triazenoimidazole carboxamide in advanced uterine sarcomas. *Cancer* 1983;52:626-32.
7. Muss HB, Bundy B, DiSaia J, Homesley HD, Fowler WC, Creasman W, et al. Treatment of recurrent or advanced uterine sarcoma: A randomized trial of doxorubicin versus doxorubicin and cyclophosphamide (a phase III trial of the Gynecologic Oncology Group). *Cancer* 1985;55:1648-53.
8. Borden EC, Amato DA, Rosenbaum C, Enterline HT, Shiraki MJ, Creech RH, et al. Randomized comparison of three adriamycin regimens for metastatic soft tissue sarcomas. *J Clin Oncol* 1987;5:840-50.
9. Borden EC, Amato DA, Edmonson JH, Ritch PS, Shiraki M. Randomized comparison of doxorubicin and vindesine to doxorubicin for patients with metastatic soft tissue sarcomas. *Cancer* 1990;66:862-7.
10. Edmonson JH, Ryan LM, Blum RH, Brooks JSJ, Shiraki M, Frytak S, et al. Randomized comparison of doxorubicin alone versus ifosfamide plus doxorubicin or mitomycin, doxorubicin, and cisplatin against advanced soft tissue sarcomas. *J Clin Oncol* 1993;11:1269-75.
11. Santoro A, Tursz T, Mouridsen H, Verweij J, Steward W, Somers R, et al. Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas: A randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. *J Clin Oncol* 1995;13:1537-45.
12. Buesa JM, Mouridsen HT, Van Oosterom AT, Verweij J, Wagener T, Steward W, et al. High dose DTIC in advanced soft tissue sarcomas in the adult. A phase II study of the EORTC Soft Tissue and Bone Sarcoma Group. *Ann Oncol* 1991;2:307-9.
13. Bramwell VHC, Mouridsen HT, Santoro A, Blackledge G, Somers R, Verwey J, et al. Cyclophosphamide versus ifosfamide: Final report of a randomized phase II trial in adult soft tissue sarcomas. *Eur J Cancer Clin Oncol* 1987;23:311-21.
14. Stuart-Harris RC, Harper PG, Parsons CA, Kaye SB, Mooney CA, Gowing NF, et al. High dose alkylation therapy using ifosfamide infusion with mesna in the treatment of adult advanced soft tissue sarcoma. *Cancer Chemother Pharmacol* 1983;11:69-72.
15. Antman KH, Ryan L, Elias A, Sherman D, Grier HE. Response to ifosfamide and mesna: 124 previously treated patients with metastatic or unresectable sarcoma. *J Clin Oncol* 1989;7:126-31.

16. Demetri GD, Elias AD. Results of single agent and combination chemotherapy for advanced soft tissue sarcomas: implications for decision making in the clinic. *Hematol Oncol Clin North Am* 1995;9:765-85.
17. Bramwell VH. Chemotherapy for metastatic soft tissue sarcomas - another full circle? *Br J Cancer* 1991;64:7-9.
18. Yap B-S, Benjamin RS, Burgess MA, Murphy WK, Sinkovics JG, Bodey GP. A phase II evaluation of methyl CCNU and actinomycin D in the treatment of advanced sarcomas in adults. *Cancer* 1981;47:2807-9.
19. Spielmann M, Sevin D, Le Chevalier T, Subirana R, Contesso G, Génin J, et al. Second line treatment in advanced sarcomas with vindesine (VDS) and cisplatin (DDP) by continuous infusion (CI). [Abstract]. *Proc Am Soc Clin Oncol* 1988;7:276. Abstract 1072.
20. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The Practice Guidelines Development Cycle: A conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13:502-12.
21. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
22. Mouridsen H, Bastholt L, Somers R, Santoro A, Bramwell V, Mulder J, et al. Adriamycin versus Epirubicin in advanced soft tissue sarcomas. A randomized phase II/phase III study of the EORTC soft tissue and bone sarcoma group. *Eur J Cancer Clin Oncol* 1987; 23:1477-83.
23. Nielsen OS, Dombernowsky P, Mouridsen H, Crowther D, Verweij J, Buesa J, et al. High-dose epirubicin is not an alternative to standard-dose doxorubicin in the treatment of advanced soft tissue sarcomas. A study of the EORTC soft tissue and bone sarcoma group. *Br J Cancer* 1998;78:1634-9.
24. Jelic S, Kovcin V, Milanovic N, Babovic N, Kreacic M, Ristovic Z, et al. Randomized study of high-dose epirubicin versus high-dose epirubicin-cisplatin chemotherapy for advanced soft tissue sarcoma. *Eur J Cancer* 1997;33:220-5.
25. Van Glabbeke M, van Oosterom A, Oosterhuis J, Mouridsen H, Crowther D, Somers R, et al. Prognostic factors for the outcome of chemotherapy in advanced soft tissue sarcoma: An analysis of 2,185 patients treated with anthracycline-containing first-line regimens - a European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. *J Clin Oncol* 1999;17:150-7.
26. Antman K, Crowley J, Balcerzak SP, Rivkin SE, Weiss GR, Elias A, et al. An Intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. *J Clin Oncol* 1993;11:1276-85.
27. Bramwell VHC, Mouridsen HT, Mulder JH, Somers R, Van Oosterom AT, Santoro A, et al. Carminomycin vs adriamycin in advanced soft tissue sarcomas: An EORTC randomised phase II study. *Eur J Cancer Clin Oncol* 1983;19:1097-104.