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Evidence-based Series # 11-4

Ifosfamide-based Combination Chemotherapy in Advanced Soft Tissue Sarcoma

*S Verma, M Blackstein, J Younus, AE Haynes,
and members of the Sarcoma Disease Site Group*

Report Date: April 11, 2006

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Section 1: Clinical Practice Guideline

Section 2: Systematic Review

Section 3: Guideline Development and External Review - Methods and Results

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Sarcoma Disease Site Group

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Evidence-based Series # 11-4: Section 1

Ifosfamide-based Combination Chemotherapy in Advanced Soft Tissue Sarcoma: A Clinical Practice Guideline

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and members of the Sarcoma Disease Site Group*

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

Report Date: April 11, 2006

Questions

1. In adult patients with inoperable locally advanced or metastatic soft tissue sarcoma, do combination chemotherapy regimens containing ifosfamide have an advantage in terms of response rate, time to progression, or survival, compared with similar regimens without ifosfamide, when used as first-line therapy?
2. What are the adverse effects and effects on quality of life of ifosfamide-containing combination chemotherapy, compared with similar regimens without ifosfamide?

Recommendation

- In patients with metastatic soft tissue sarcoma, the addition of ifosfamide to standard first-line doxorubicin containing regimens is not recommended over single-agent doxorubicin. However, in patients with symptomatic, locally-advanced, or inoperable soft tissue sarcoma, in whom tumour response might potentially result in reduced symptomatology or render a tumour resectable, it is reasonable to use ifosfamide in combination with doxorubicin.

Qualifying Statements

- In combination with doxorubicin-containing regimen, the dose of ifosfamide should not exceed 7.5 g/m² given as either a split bolus or continuous infusion.

Key Evidence

- Evidence was available from three randomized phase III trials and 22 single-arm phase II trials. Three randomized controlled trials of ifosfamide-containing versus non-ifosfamide-containing chemotherapy in patients with metastatic or inoperable locally advanced soft tissue sarcoma have been reported to date.
- Two meta-analysis of published data from three randomized trials were conducted (N=1039). In two of the trials, patients were randomized to one of three chemotherapy

regimens; however, only two of the three arms in both trials were included in the meta-analysis.

- A small, statistically significant improvement in tumour response rate was observed with ifosfamide-containing chemotherapy compared to non-ifosfamide-containing chemotherapy (relative risk, 1.52; 95% confidence interval, 1.11 to 2.08; p=0.009).
- Meta-analysis of published one-year mortality rates from those randomized trials did not detect a significant difference between ifosfamide and non-ifosfamide-containing chemotherapy (relative risk, 0.98; 95% confidence interval, 0.85 to 1.13; p = 0.28).
- Higher rates of adverse events, particularly grade 3-4 myelosuppression were observed in patients who received regimens that contained ifosfamide. A higher rate of toxic deaths was reported in two of the three randomized trials, for the ifosfamide-containing regimen.

Future Research

- Future research should investigate the use of ifosfamide as part of a neo-adjuvant chemotherapy regimen for patients with inoperable locally advanced STS in order to determine if it can render the tumours in these patients resectable.
- Future trials should include measures of quality of life.

Related Guidelines

- Practice Guideline Report #11-1: *Doxorubicin-Based Chemotherapy for the Palliative Treatment of Adult Patients With Locally Advanced or Metastatic Soft Tissue Sarcoma* [completed guideline]. This guideline recommends that "single-agent doxorubicin is an appropriate first-line chemotherapy option for advanced or metastatic soft tissue sarcoma."
- Practice Guideline Report #11-5: *Dose-Intensive Chemotherapy With Growth Factor or Autologous Bone Marrow/Stem Cell Transplant Support in Advanced or Metastatic Adult Soft Tissue Sarcoma* [completed guideline].

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Evidence-based Series # 11-4: Section 2

Ifosfamide-based Combination Chemotherapy in Advanced Soft Tissue Sarcoma: A Systematic Review

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

Report Date: April 7, 2006

QUESTIONS

1. In adult patients with inoperable locally advanced or metastatic soft tissue sarcoma (STS), do combination chemotherapy regimens containing ifosfamide have an advantage in terms of response rate, time to progression, or survival compared with similar regimens without ifosfamide when used as first-line therapy?
2. What are the adverse effects and effects on quality of life of ifosfamide-containing combination chemotherapy, compared with similar regimens without ifosfamide?

INTRODUCTION

The prognosis for patients with inoperable or metastatic STS remains grim. Although the surgical resection of pulmonary metastases may be curative in 15% to 30% of patients with isolated slow-growing metastases (1,2), the majority of patients receive chemotherapy for palliative purposes. Doxorubicin is one of the most active single agents in STS, with a response rate between 15% and 30% observed in various clinical trials (3). The Sarcoma Disease Site Group (DSG) of the PEBC systematically reviewed randomized trials that compared doxorubicin-based combination chemotherapy with doxorubicin as a single agent for an earlier practice guideline (3). Meta-analysis of published data from those trials detected no significant differences in response rate (odds ratio [OR], 0.79; 95% confidence interval [CI], 0.60 to 1.05; $p=0.10$) or survival (OR, 0.84; 95% CI, 0.67 to 1.06; $p=0.13$) between combination and single-agent therapy (OR <1.0 favours combination therapy for both outcomes). Single-agent doxorubicin is therefore considered an acceptable standard of care in patients with metastatic or inoperable STS who are candidates for chemotherapy.

Ifosfamide is an analogue of cyclophosphamide with one chloroethyl group shifted to the ring nitrogen atom. Several preclinical phase I and phase II trials with this drug have demonstrated an apparent lack of cross-resistance to cyclophosphamide (4,5,6). Ifosfamide has documented activity in patients who have received prior treatment with, or who have progressed on, doxorubicin (6-9). A number of studies have suggested a schedule and dose-response relationship for ifosfamide in metastatic STS (9-11). Ifosfamide has also been

assessed in combination with other drugs such as doxorubicin and DTIC (9,12,13); results of such studies have led some authors to suggest that polychemotherapy utilizing 'appropriate doses' of ifosfamide and doxorubicin may represent the 'most effective systemic treatment' in this population. In the meta-analysis referred to above (3), there were ten doxorubicin-based combination regimens evaluated in eight randomized trials. Only two of those contained ifosfamide, accounting for 352 of the 2281 patients eligible for the meta-analysis. As there are limited effective therapeutic options available for patients with metastatic STS, the Sarcoma DSG felt there was a need to more specifically evaluate the potential benefits of ifosfamide-containing combination chemotherapy in this setting.

METHODS

This systematic review was developed by CCO's PEBC, using the methods of the Practice Guidelines Development Cycle (14). Evidence was selected and reviewed by one member of the PEBC Sarcoma DSG and methodologists.

This systematic review is a convenient and up-to-date source of the best available evidence on ifosfamide-based combination chemotherapy for patients with inoperable locally advanced or metastatic STS. The body of evidence in this review is primarily comprised of mature randomized controlled trial data. That evidence forms the basis of a clinical practice guideline developed by the Sarcoma DSG. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of CCO and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

MEDLINE (1966 to July 2005), EMBASE (1980 to July 2005), and the Cochrane Library (2004, Issue 3) databases were searched. Disease-specific search terms "sarcoma" (exploded Medical Subject Heading (MeSH) and text word) and "soft tissue" (as text words) were combined with treatment-specific terms "ifosfamide" (MeSH and text word), "ifosphamide", "iphosphamide" and "ifex" (text words). These terms were then combined with search terms for the following publication types and study designs: practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, phase II clinical trials, and phase III clinical trials.

In addition, conference proceedings of the American Society of Clinical Oncology (1997-Spring 2005) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (<http://mdm.ca/cpgsnew/cpgs/index.asp>) and the National Guidelines Clearinghouse (<http://www.guideline.gov/index.asp>) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by one reviewer, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

Inclusion Criteria

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

1. They were published reports or abstracts of randomized controlled trials (RCTs) comparing combination chemotherapy regimens containing ifosfamide with regimens without ifosfamide in adult patients with locally advanced or metastatic STS.

Although data from RCTs provided the primary evidence for this systematic review, single-arm phase II trials reporting on treatment with ifosfamide-containing combination chemotherapy regimens in adult patients with locally advanced or metastatic STS were also eligible. We also elected to examine the outcomes of phase II trials in order to obtain data on response and toxicity for different doses and schedules

of ifosfamide-based treatment and on ifosfamide chemotherapy as second-line treatment, which were not available from the limited number of RCTs.

2. They reported data on time-to-progression or overall survival, in addition to the objective tumour response rate.

Exclusion Criteria

Articles were excluded if they were:

1. Trials of dose-intensive chemotherapy with growth factor or autologous bone marrow/stem cell transplant support (these will be included in a separate guideline);
2. Letters or editorials.
3. Published in a language other than English.
4. Trials of patients with pediatric sarcomas, Ewing's sarcoma or bone sarcoma.
5. Trials where patients were given concurrent radiotherapy or local regional modalities such as surgery, which might have influenced response or survival.

Synthesizing the Evidence

To estimate the effect of ifosfamide-containing combination chemotherapy on response rate and survival in patients with locally advanced or metastatic STS, published data from RCTs were pooled in a meta-analysis by the guideline developers. Objective tumour response data (i.e., number of complete and partial responses) were obtained from the text of published trial reports, and one-year mortality data were extracted from published survival curves. The numbers of eligible patients were used as denominators for all pooled analyses. One year was selected as the time point at which to pool mortality data, because the expected median survival of patients with inoperable locally advanced or metastatic STS is nine to 12 months. Data were pooled and analyzed using the MetaView analysis component of the Cochrane Collaboration Review Manager 4.2 software (15). The results of the meta-analysis are expressed as a relative risk (RR) with a corresponding 95% confidence interval (CI). For tumour response, a relative risk >1.0 indicates that patients in the experimental treatment group (ifosfamide-based combination chemotherapy) had a higher probability of a complete or partial response compared with the control group (non-ifosfamide chemotherapy); conversely, a relative risk of response <1.0 favours the control group (non-ifosfamide chemotherapy).

For one-year mortality, a RR <1.0 indicates that the patients in the experimental treatment group (ifosfamide-based combination chemotherapy) experienced higher survival rates than the control group (non-ifosfamide chemotherapy). Data were analyzed using the random effects model (Mantel-Haenszel). Heterogeneity was considered to be significant when p was less than 0.1 on the chi-square test for statistical heterogeneity.

Response rates from phase II trials of combination chemotherapy that contained ifosfamide and an anthracycline in patients who had not received prior chemotherapy were also pooled. The overall treatment effect was estimated by calculating the weighted mean response rate across studies. Response rates (p) for individual trials were weighted by the inverse variance, where the variance was calculated as $[p(p-1)]/N$.

RESULTS

Literature Search Results

The literature search identified three randomized phase III trials (12,13,16) and 23 single-arm phase II trials (5,9,17-37) that met the inclusion criteria for this systematic review of the evidence (Table 1).

All three RCTs and 16 of the phase II trials used ifosfamide with an anthracycline (doxorubicin or epirubicin). The remaining seven phase II studies used ifosfamide in combinations that did not include an anthracycline. Two randomized trials that compared doxorubicin alone with doxorubicin plus ifosfamide (12,13) were also included in our previous

guideline on doxorubicin-based combination chemotherapy versus single-agent doxorubicin (3); both trials included a third treatment group who received combination chemotherapy that included doxorubicin but not ifosfamide. The third randomized trial compared doxorubicin plus DTIC (dacarbazine) with and without ifosfamide (16). The RCTs and most of the phase II trials used doses of ifosfamide of 7.5 g/m² or less.

Table 1. Clinical trials of ifosfamide-containing chemotherapy included in this systematic review of the evidence.

Ifosfamide combination evaluated (ifosfamide dose) vs. control treatments for randomized trials	Trial	Number enrolled
<i>Randomized trials (phase III)</i>		
doxorubicin + ifosfamide 5 g/m ² (24 hour infusion) vs. doxorubicin alone	Santoro, 1995 (12)	749
vs. doxorubicin + cyclophosphamide + vincristine + DTIC		
doxorubicin + ifosfamide 3.75 g/m ² /day (4 hour infusion, 2 days) vs. doxorubicin alone	Edmonson, 1993 (13)	279
vs. mitomycin + doxorubicin + cisplatin		
doxorubicin + DTIC + ifosfamide 6 g/m ² (3 day infusion) vs. doxorubicin + DTIC	Antman, 1993 (16)	374
<i>Single-cohort phase II trials of ifosfamide with an anthracycline (doxorubicin or epirubicin)</i>		
	Comandone, 2000 (17)	42
	Chevallier, 1993 (18)	30
	Schutte, 1993 (19)	203
doxorubicin or epirubicin + ifosfamide (≤ 7.5 g/m ²)	Toma, 1993 (20)	46
	Loehrer, 1989 (21)	42
	Cantwell, 1988 (22)	16
	Mansi, 1988 (23)	54
doxorubicin or epirubicin + DTIC + ifosfamide (≤ 7.5 g/m ²)	Elias, 1990 (9)	105
	Gonzalez-Manzano, 1993 (24)	27
	Bokemeyer, 1992 (25)	28
	Bramwell, 1989 (26)	43
doxorubicin + vincristine + DTIC + ifosfamide (≤ 7.5 g/m ²)	Wiklund, 1992 (27)	37
doxorubicin or epirubicin + cisplatin + ifosfamide (≤ 7.5 g/m ²)	Shimizu, 2002 (28)	30
	[abstract]	30
	Levy, 1998 (29) [abstract]	
doxorubicin + cisplatin + 5-FU + ifosfamide (≤ 7.5 g/m ²)	Jager, 1996 (30)	58
epirubicin + ifosfamide (> 7.5 g/m ²)	Frustaci, 1993 (31)	66
<i>Single-cohort phase II trials of ifosfamide in non-anthracycline combinations</i>		
etoposide + ifosfamide (2g/m ² /day over 24 hours, 5 days)	Yalçin, 1998 (5)	26
etoposide + ifosfamide (1.8 g/m ² /day over 2 hours, 5 days)	Kawai, 2004 (32) [abstract]	22
etoposide + ifosfamide (2.5 g/m ² /day over 2 hours, 3 days)	Edmonson, 1989 (33)	44
etoposide + ifosfamide (2.0 g/m ² /day over 1 hour, 4 days)	Blair, 1994 (34)	21
etoposide + ifosfamide (1.5 g/m ² /day over 2 hours, 3 days)	Saeter, 1997 (35)	92
etoposide + cisplatin + ifosfamide (2 g/m ² , 2 days)	Papai, 2000 (36)	104
cisplatin + ifosfamide (2.5 g/m ² /day over 24 hours, 3 days)	Budd, 1993 (37)	39

Notes: 5-FU – 5-fluorouracil; DTIC – dacarbazine; vs. – versus..

Outcomes

Randomized Controlled Trials

Tables 2 through 4 summarize the three RCTs that compared a combination chemotherapy regimen that included ifosfamide with a similar regimen that did not include ifosfamide (12,13,16). All regimens containing ifosfamide utilized an appropriate dose of mesna. Both the experimental and control regimens included doxorubicin. Patients who had received prior chemotherapy were excluded from all three trials. None of the trials was double blind or used an intention-to-treat analysis, but central randomization was used to ensure the concealment of allocation prior to randomization in the trial by Santoro et al (12). Only the report of the largest trial, by Santoro et al, included a justification of sample size, and the sample size target was met (12). None of the RCTs reported data on quality of life. All three trials entered patients with relatively good performance status (PS), although different measures for PS were used for the individual trial inclusion criteria.

Santoro et al (12) randomized 749 patients to chemotherapy consisting of i) single-agent doxorubicin, ii) doxorubicin combined with ifosfamide, or iii) a combination of cyclophosphamide, vincristine, doxorubicin, and dacarbazine (CYVADIC). The CYVADIC arm was closed early because an interim analysis "did not show any benefit for this arm." Eighty-nine percent of randomized patients were eligible, 88% were included in the survival analysis in the trial report, and 81% were assessable for tumour response. No statistically significant differences in response rate, response duration, overall survival, or time-to-progression were detected among the three treatment groups (Table 3). Adverse effects were reported in similar proportions of patients in all three groups, with the exception of leucopenia and cardiac effects (Table 4). Grade 4 leucopenia was significantly more common with the doxorubicin and ifosfamide combination compared to single-agent doxorubicin ($p < 0.001$). Adverse cardiac effects were also significantly more frequent with doxorubicin plus ifosfamide; however, no p-value was reported. The rate of grade 3 or 4 nausea and vomiting was not reported for the doxorubicin plus ifosfamide group, but 94% of patients on this combination reported some nausea or vomiting, compared with 84% on single-agent doxorubicin and 96% on the CYVADIC combination. More renal insufficiency and hematuria (grade 3 in two patients) was observed in the ifosfamide group, compared to the other two groups. No treatment-related deaths were reported in the trial.

Edmonson et al (13) randomized 279 patients to one of the following three treatments: i) single-agent doxorubicin, ii) doxorubicin combined with ifosfamide, or iii) doxorubicin combined with mitomycin and cisplatin. Ninety-four percent of randomized patients were eligible, and all but one eligible patient was included in outcome analyses. The overall response rate was significantly higher with doxorubicin plus ifosfamide, compared with single-agent doxorubicin ($p = 0.03$), but was similar to doxorubicin/mitomycin/cisplatin. There were no significant differences in overall survival (Table 3). Treatment-related toxicity was substantial in that trial, with grade 4 or 5 adverse events occurring at some time during treatment in 21% of patients receiving doxorubicin, 70% receiving doxorubicin plus ifosfamide, and 33% receiving the three-drug combination of doxorubicin, mitomycin, and cisplatin. The doxorubicin and ifosfamide regimen was significantly more myelosuppressive than either doxorubicin alone or the three-drug combination ($p = 0.01$) (Table 4). Renal toxicity was not discussed in the trial report. There were two treatment-related deaths in the doxorubicin arm, three in the doxorubicin plus ifosfamide arm, and one in the three-drug combination arm. The deaths in the doxorubicin plus ifosfamide group were due to myelosuppression-related gastrointestinal hemorrhage in one case and to unknown causes in the other two cases.

Antman et al (16) randomized 374 patients to receive either doxorubicin combined with dacarbazine (DTIC) or a combination of doxorubicin, DTIC, and ifosfamide (MAID). After 154 patients had been recruited, the dose of ifosfamide was decreased from 7.5 g/m^2 to 6 g/m^2 because of unacceptable myelosuppression with the higher dose. Ninety-one percent of

randomized patients were eligible and were included in outcome analyses. The trial report noted that there was a slight imbalance between treatment groups with respect to high-grade tumours, with a greater proportion of those tumours in the MAID group. The overall response rate ($p < 0.005$) and median time-to-progression ($p = 0.02$) were significantly improved with MAID, compared with doxorubicin plus DTIC; however, overall survival was significantly longer with doxorubicin plus DTIC ($p = 0.04$) (Table 3). The rates of severe leucopenia, granulocytopenia, thrombocytopenia, and nausea and vomiting were higher on MAID than on doxorubicin plus DTIC, but no p-values were reported (Table 4). No serious renal toxicity was observed in either group. Eight treatment-related deaths were reported in the MAID arm, compared with one in the doxorubicin and DTIC arm. The eight deaths in the ifosfamide-containing (MAID) group were all associated with grade 4 myelosuppression; seven were due to infection, and one to encephalopathy.

Table 2. Randomized controlled trials of combination regimens containing ifosfamide versus regimens without ifosfamide: Treatment and patient characteristics.

Study	Prior chemotherapy	Chemotherapy Regimen* (repeated every 3 weeks)	# enrolled # eligible # analyzed**
		doxorubicin 75 mg/m ² iv	NR 263 260
Santoro, 1995 (12)	No	doxorubicin 50 mg/m ² iv ifosfamide 5 g/m ² civ (24 hour)	NR 258 254
EORTC		CYVADIC: cyclophosphamide 500 mg/m ² iv vincristine 1.5 mg/m ² iv doxorubicin 50 mg/m ² iv DTIC 750 mg/m ² iv (30min)	NR 142 142
		doxorubicin 80 mg/m ² iv	95 90 90
Edmonso n, 1993 (13)	No	doxorubicin 30 mg/m ² /d iv for 2 days ifosfamide 3.7 g/m ² /d iv (4 hour) for 2 days	94 88 88
		mitomycin 8 mg/m ² iv doxorubicin 40 mg/m ² iv cisplatin 60 mg/m ² iv	90 85 84
Antman, 1993 (16)	No	doxorubicin 60 mg/m ² civ over 4 days DTIC 1,000 mg/m ² civ over 4 days	186 170 170
Intergroup		MAID: doxorubicin 60 mg/m ² civ over 4 days DTIC 1,000 mg/m ² civ over 4 days ifosfamide 6.0-7.5 g/m ² civ over 3 days	188 170 170

Notes: CALGB - Cancer and Leukemia Group B; civ - continuous intravenous infusion; DTIC - dacarbazine; ECOG - Eastern Cooperative Oncology Group; EORTC - European Organization for Research and Treatment of Cancer; iv - intravenously; NR - not reported; q - every; WHO - World Health Organization, d- day

* All regimens containing ifosfamide were given with an appropriate dose of mesna.

** For survival in the trial report

Table 3. Randomized controlled trials of combination regimens containing ifosfamide versus regimens without ifosfamide: clinical outcomes.

Study	Chemotherapy Regimen	Tumour Response (complete or partial)			Survival		Time-to-progression		
		Number eligible patients	Number responses (# CR)	Response Rate* (%)	Median Duration (months)	Median (months)	log-rank p-value	Median (months)	log-rank p-value
Santoro, 1995 (12)	DOX	263	56(NR)	21	10.7	12.1		7.5 ^a	
	DOX + IFOS	258	65(NR)	25	10.2	12.8	0.97	10 ^a	0.58
	CYVADIC	142	38(NR)	27	11.1	11.9		10 ^a	
Edmonson, 1993 (13)	DOX	90	18(2)	20		8.4 ^a			
	DOX + IFOS	88	30(3)	34 ^b	NR	11.5 ^a	NS	NR	NR
	DOX/mitomycin /cisplatin	85	27(6)	32		9.4 ^a			
Antman, 1993 (16)	DOX + DTIC	170	29(4)	17	8	13	0.04	4	0.02
	MAID	170	55(4)	32 ^c	10	12		6	

Notes: DOX - doxorubicin; IFOS - ifosfamide; CYVADIC - cyclophosphamide + vincristine + doxorubicin + dacarbazine; CR - complete response; DTIC - dacarbazine; MAID - mesna + doxorubicin + ifosfamide + dacarbazine.

NS – Not Significant

NR – Not Reported

* (# partial responses + # complete responses) /# eligible patients.

^a Data estimated from published survival curve.

^b Significantly higher response rate than doxorubicin alone (p=0.03).

^c Significantly higher response rate than doxorubicin + DTIC (p<0.005)

Table 4. Randomized controlled trials of combination regimens containing ifosfamide versus regimens without ifosfamide: percentage of patients with adverse effects.

Study	Chemotherapy Regimen	G3 or greater hematological toxicity	G3 or 4 nausea/vomiting	Neurotoxicity	Cardiac toxicity	Renal toxicity	No. toxic deaths
Santoro, 1995 (12)	DOX	Leucopenia (G4) 13 Thrombocytopenia 4	17	2	2	0	0
	DOX +IFOS	Leucopenia (G4) 32 ^a Thrombocytopenia 6	NR	10 (2% grade 3/4)	6 (2% grade 3)	4	0
	CYVADIC	Leucopenia (G4) 15 Thrombocytopenia 10	40	14	1	1	0
Edmonson, 1993 (13)	DOX	Myelosuppression 53 Leucopenia (G4) 9	7	NR	NR	NR	2
	DOX + IFOS	Myelosuppression 80 ^b Leucopenia (G4) 44	18	NR	NR	NR	3
	DOX/ mitomycin /cisplatin	Myelosuppression 55 Leucopenia (G4) 5	17	NR	NR	NR	1
Antman, 1993 (16)	DOX + DTIC	Granulocytopenia 38 Leucopenia 32 Thrombocytopenia 4	9	0	1	0	1
	MAID	Granulocytopenia 79 Leucopenia 86 Thrombocytopenia 26	19	7	0	0	8

Notes: CYVADIC - cyclophosphamide + vincristine + doxorubicin + dacarbazine; DOX - doxorubicin; DTIC - dacarbazine; IFOS - ifosfamide; MAID - mesna + doxorubicin +ifosfamide + dacarbazine, G – grade, No. – number, NR – Not reported

^a Grade 4 leucopenia significantly more frequent with DOX + IFOS compared with DOX alone (p<0.001).

^b Myelosuppression significantly more frequent with DOX + IFOS compared with DOX and DOX/mitomycin/cisplatin (p=0.01).

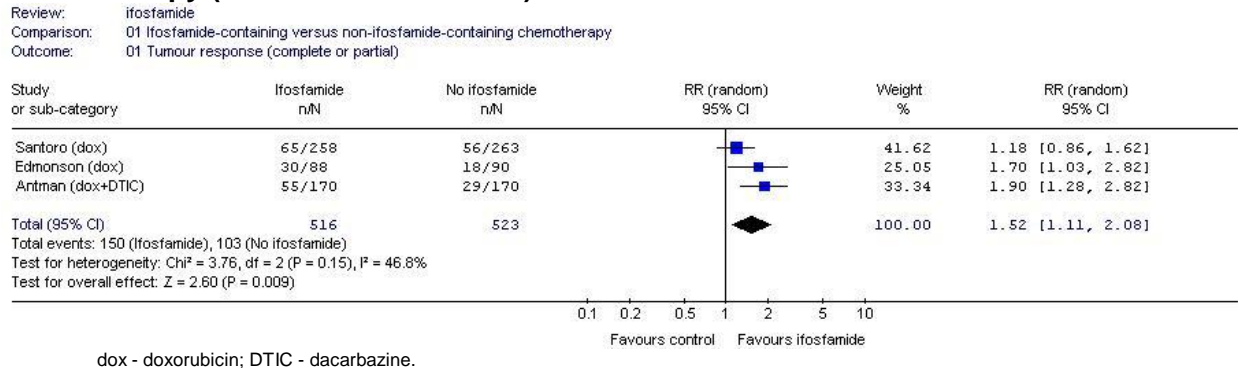
Meta-analysis of Data from Randomized Controlled Trials

The guideline developers pooled published tumour response and one-year mortality data from the three RCTs described above (12,13,16). Summary data based on 1612 eligible patients were available for pooling. Two trials (12,13) compared three treatment regimens each. Both of those trials included a regimen of doxorubicin alone and a regimen of doxorubicin and ifosfamide. The third regimen from both trials was not included in the meta-analysis as both of those regimens contained chemotherapy agents in addition to doxorubicin and neither contained ifosfamide. As the purpose of this guideline is to determine if the addition of ifosfamide to other chemotherapy agents improves patient outcomes, the comparison of interest is between chemotherapy regimens, where the only difference in chemotherapy agents is the presence or absence of ifosfamide. The results illustrated in Figures 1 and 2 were obtained using the random effects model.

Tumour response

The pooled analysis of objective tumour response from the relevant chemotherapy regimens of the three trials detected a significant difference between ifosfamide-containing chemotherapy and non-ifosfamide-containing chemotherapy with the random effects model (RR, 1.52, in favour of ifosfamide; 95% CI, 1.11 to 2.08; p=0.009) (Figure 1). Statistical heterogeneity was moderate but not significant across the three trials (chi square, 3.76; p=0.15).

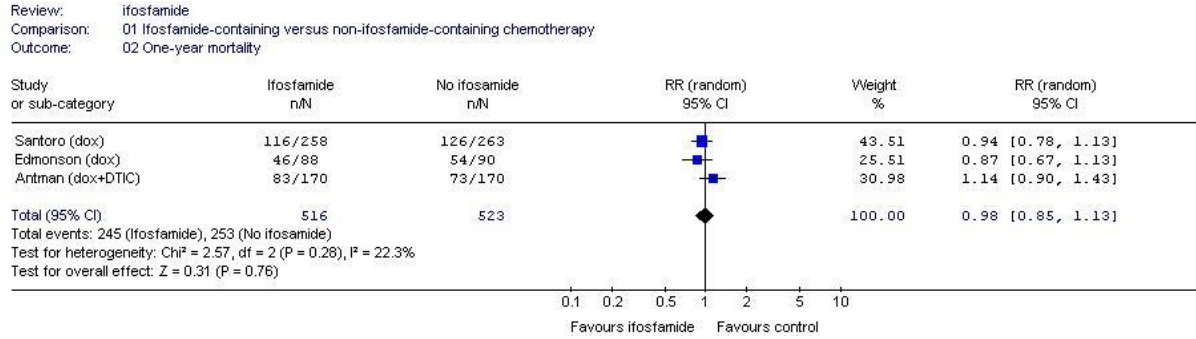
Figure 1. Meta-analysis of published tumour response data from randomized controlled trials of ifosfamide-containing chemotherapy versus non-ifosfamide-containing chemotherapy (random effects model).



Survival

The pooled analysis of one-year mortality data did not detect a significant difference between ifosfamide-containing chemotherapy and non-ifosfamide-containing chemotherapy (RR, 0.98; 95% CI, 0.85 to 1.13, p=0.76) (Figures 2). There was no significant heterogeneity among the three trials (chi square, 2.57; p=0.28). Results were similar when the analyses was repeated using the fixed effect model.

Figure 2. Meta-analysis of published one-year mortality data from randomized controlled trials of ifosfamide-containing chemotherapy versus non-ifosfamide-containing chemotherapy (random effects model).



dox - doxorubicin; DTIC - dacarbazine.

Phase II Trials

A number of trials have used ifosfamide at a dose analogous to that used in the RCTs ($\leq 7.5 \text{ g/m}^2$). However, the literature search also identified phase II trials that used ifosfamide at doses $> 7.5 \text{ g/m}^2$, and those are examined separately.

Prior chemotherapy was not described for one trial, reported in abstract form by Levy et al (29). The remaining 22 phase II trials can be divided into four groups, based on prior chemotherapy, ifosfamide dose, and type of ifosfamide-based chemotherapy:

Chemotherapy containing ifosfamide and an anthracycline

The 16 phase II trials that evaluated chemotherapy containing both ifosfamide and an anthracycline are of primary interest for this practice guideline (9,17-31). Those are described in detail in Tables 5-7.

Table 5. Phase II trials of combination regimens containing ifosfamide and an anthracycline.

Study	# enrolled (evaluated)	Chemotherapy Regimen* (repeated every 3 or 4 weeks)
No prior chemotherapy		
<i>Ifosfamide dose ≤ 7.5 g/m²</i>		
Comandone, 2000 (17)	42 (40)	ifosfamide 1.2 g/m ² iv days 1-5 + doxorubicin 30 mg/m ² iv days 1,2
Chevallier, 1993 (18)	30 (27)	ifosfamide 2.5 g/m ² /day iv (6 hour) days 1,2 + epirubicin 100 mg/m ² iv day 1
Schutte, 1993 (19)	203 (175)	ifosfamide 5 g/m ² iv (24 hour) + doxorubicin 50 mg/m ² iv
Loehrer, 1989 (21)	42 (42)	ifosfamide 5 g/m ² iv (24 hour) + doxorubicin 60 mg/m ² iv
Elias, 1990 (9)	105 (97)	ifosfamide 2.5 g/m ² /day civ + doxorubicin 20 mg/m ² /day iv + DTIC 300 mg/m ² /day iv days 1-3
Bokemeyer, 1992 (25)	28 (27)	ifosfamide 6 g/m ² iv (24 hour) day 15 + epirubicin 100 mg/m ² day 1 + DTIC 500 mg/m ² days 1,2
Bramwell, 1989 (26)	43 (40)	ifosfamide 5 g/m ² iv (24 hour) + doxorubicin 50 mg/m ² iv + DTIC 850 mg/m ² iv
Shimizu, 2002 (28) [abstract]	30 (30)	ifosfamide 700 mg/m ² iv (2 hour) days 1-4 + epirubicin 50 mg/m ² iv day 7 + cisplatin 10 mg/m ² iv days 1-7
Jager, 1996 (30)	58 (56)	ifosfamide 4 g/m ² iv (6 hour) day 1 + doxorubicin 50 mg/m ² iv day 1 + 5-FU 500 mg/m ² iv days 1,2 + cisplatin 100 mg/m ² iv day 2
<i>Ifosfamide dose >7.5 g/m²</i>		
Frustaci, 1993 (31)	66 (64)	ifosfamide 1.8 g/m ² /day iv (1 hour) days 1-5 + epirubicin 75 mg/m ² iv day 1
6%-17% of patients had prior chemotherapy		
<i>Ifosfamide dose ≤ 7.5 g/m²</i>		
Toma, 1993 (20)	46 (45)	ifosfamide 1.2 g/m ² /day iv (2 hour) days 1-5 + epirubicin 50-100 mg/m ² iv day 1
Cantwell, 1988 (22)	16 (16)	ifosfamide 5 g/m ² iv (24 hour) day 1 + doxorubicin 40 mg/m ² iv day 1
Mansi, 1988 (23)	54 (50)	ifosfamide 5 g/m ² iv (24 hour) day 1 + doxorubicin 40 mg/m ² (first 28 patients) or 60 mg/m ² (subsequent 22 patients) iv day 1
Gonzalez- Manzano, 1993 (24)	27 (25)	ifosfamide 1.5 g/m ² /day iv (1 hour) days 1-3 + doxorubicin 50 mg/m ² iv day 1 + DTIC 400 mg/m ² /day iv days 1-3 + amphotericin B 25 mg/m ² iv
Wiklund, 1992 (27)	37 (24)	ifosfamide 1 g/m ² /day iv (2 hour) days 1-5 + doxorubicin 50 mg/m ² iv day 1 + DTIC 250 mg/m ² /day iv days 1-5 + vincristine 1.5 mg/m ² iv day 1
Prior chemotherapy unknown		
Levy, 1998 (29) [abstract]	30 (29)	ifosfamide 2.5 g/m ² /day civ days 1-3 + doxorubicin 60 mg/m ² iv day 1 + cisplatin 60 mg/m ² iv day 2

Notes: 5-FU, 5-fluorouracil; civ - continuous intravenous infusion; DTIC - dacarbazine; iv - intravenously; sc - subcutaneously.

* Regimens containing ifosfamide were administered with appropriate doses of mesna.

In 10 of 16 phase II trials of ifosfamide- and anthracycline-containing chemotherapy, patients had not received prior chemotherapy (9,17-19,21,25,26,28,30,31), which was also an entry criterion for the RCTs discussed above. All but one of those 10 trials used a dose of ifosfamide $<7.5 \text{ g/m}^2$ (9,17-19,21,25,26,28,30) as did the RCTs. There was considerable variation in drugs, doses, and schedules among the clinical trials, but one phase II trial, by Schutte et al (19), employed the same ifosfamide plus doxorubicin regimen as the RCT by Santoro et al (12).

Clinical outcomes for combination chemotherapy containing ifosfamide and an anthracycline in patients *without* prior chemotherapy

Table 6a lists ten phase II trials that evaluated ifosfamide primarily in patients without prior chemotherapy. One patient in each of two trials had received prior chemotherapy but were still included in that category (17,21). The pooled response rate across all ten trials was 34%.

Nine trials used doses of ifosfamide $<7.5 \text{ g/m}^2$ given with an anthracycline, either doxorubicin or epirubicin (9,17-19,21,25,26,28,30). In three of those trials, DTIC (dacarbazine) was added to the chemotherapy regimen (9,25,26), and, in two trials, cisplatin was used in addition to ifosfamide and anthracycline (30,31). The pooled response rate across those nine trials was 35%. Median survival ranged from 8 to 16 months.

One trial that used ifosfamide at a dose greater than 7.5 mg/m^2 in combination with epirubicin (31) observed a response rate of 27% and median survival of 13 months.

Clinical outcomes for combination chemotherapy containing ifosfamide and an anthracycline in patients *with* prior chemotherapy

The results of five phase II trials of ifosfamide and an anthracycline in which 6-17% of patients had received previous chemotherapy (20,22-24,27) and one additional trial where the prior chemotherapy agent or other treatment was not specified (29) are summarized in Table 6b. In the study by Toma et al, no responses were observed among a subgroup of six patients, treated with ifosfamide plus epirubicin, who had received previous chemotherapy (20). Cantwell et al reported that the only patient with prior chemotherapy died due to treatment and, during the autopsy, found that the patient had a complete response (22). In the study reported by Mansi et al, three of the eight patients with prior chemotherapy had a partial response (23). In the study by Gonzalez-Manzano et al, one of three patients with prior chemotherapy had a partial response to ifosfamide/doxorubicin/cisplatin (24). Wiklund et al reported that one of four patients with prior chemotherapy achieved a partial response (27). Levy et al did not report the response in patients who had received previous chemotherapy treatment (29).

Adverse events in phase II trials of combination chemotherapy containing ifosfamide and an anthracycline

Toxicity data from phase II trials of combination chemotherapy that included both ifosfamide and an anthracycline are summarized in Table 7.

Grade 3 or 4 hematological toxicity was observed in all of the trials except for the one reported by Cantwell et al. Febrile neutropenia was reported in seven of 16 trials (9,24-26,29-31). Rates of grade 3 or 4 nausea and vomiting ranged from 7% to 64%. Between 3% and 7% of patients in six trials developed grade 2-4 neurotoxicity (9,19-21,25,26), which was associated with coma in two patients (21,26). One patient who had received prior treatment with doxorubicin (21) and three without prior chemotherapy developed congestive heart failure (25,27). Renal toxicity was not reported consistently. Grade 3 adverse renal events were reported for three patients in the trial by Schutte et al (19) and one in the trial by Bokemeyer et al (25). One patient in the trial by Elias et al developed reversible acute renal insufficiency, and another had severe proximal renal tubular acidosis (9). One patient in the trial reported by Cantwell et al developed renal failure and subsequently died.

Nine treatment-related deaths were reported in nine phase II trials. Causes of death included infection in four cases (9,19,27,30), cardiac failure in one (25), seizures and coma in one (21), subarachnoid hemorrhage related to thrombocytopenia in one (24), renal failure and septicaemia in one (22), and severe neutropenia in one (23).

Table 6a. Phase II trials of combination regimens containing ifosfamide and an anthracycline: Clinical outcomes in patients without prior chemotherapy.

Study	# responses /# eligible (#CR)	Response rate* (%)	Median duration of response (months)	Median survival (months)	Median time- to- progression (months)
<i>Ifosfamide dose ≤ 7.5 g/m²</i>					
<i>Ifosfamide (≤ 7.5 g/m²) + anthracycline</i>					
Comandone, 2000 (17)	12/42 (6)	29	NR	7.6	7
Chevallier, 1993 (18)	13/28 (0)	46	NR	9.2	6.2
Schutte, 1993 (19)	61/203 (16)	30	NR	13.5	6.7
Loehrer, 1989 (21)	15/42 (3)	36	7	8	NR
<i>Ifosfamide (≤ 7.5 g/m²) + anthracycline + dacarbazine</i>					
Elias, 1990 (9)	48/105 (11)	46	NR	16	CR 10.4 PR 9.5 SD 7.9
Bokemeyer, 1992 (25)	8/28 (0)	29	8.5	NR	5.5
Bramwell, 1989 (26)	10/41 (2)	24	PR 3.2	12	NR
<i>Ifosfamide (≤ 7.5 g/m²) + anthracycline + cisplatin</i>					
Shimizu, 2002 (28) [abstract]	18/30 (5)	60	NR	16	NR
<i>Ifosfamide (≤ 7.5 g/m²) + anthracycline + with cisplatin + 5-FU</i>					
Jager, 1996 (30)	17/58 (1)	29%	18.1	11.8	4.5
<i>Ifosfamide dose >7.5 g/m²</i>					
Frustaci, 1993 (31)	18/66 (6)	27	CR 10 PR 9	13	NR

Notes: CR - complete response; NR - not reported; PR - partial response; SD - stable disease, 5-FU – 5-Fluorouracil.

* (# partial responses + # complete responses)/# eligible patients.

Table 6b. Phase II trials of combination regimens containing ifosfamide and an anthracycline: Clinical outcomes in patients with and without prior chemotherapy.

Study	# responses / # eligible (#CR)	Response rate*	Median duration of response (months)	Median survival (months)	Median time-to-progression (months)
<i>Ifosfamide (≤ 7.5 g/m²) + anthracycline</i>					
Toma, 1993 (20)	17/46 (4)	37%	CR 17.5 PR 10	10	NR
Cantwell, 1988 (22)	6/16 (1)	38%	NR	NR	NR
Mansi, 1988 (23)	11/54 (3)	20%	CR 14 PR 6	CR 17 PR 12 SD 11 PD 5	SD 3
<i>Ifosfamide (≤ 7.5 g/m²) + anthracycline + dacarbazine</i>					
Gonzalez-Manzano, 1993 (24)	12/27 (1)	44%	CR 2 PR 6.6	12	NR
<i>Ifosfamide (≤ 7.5 g/m²) + anthracycline + dacarbazine + vincristine</i>					
Wiklund, 1992 (27)	11/24 (4)	46%	NR	10	5
<i>Ifosfamide (≤ 7.5 g/m²) + anthracycline + cisplatin</i>					
Levy, 1998 (29) [abstract]	15/30 (5)	50%	NR	18	NR

Notes: CR - complete response; NR - not reported; PD - progressive disease; PR - partial response; SD - stable disease.

* (# partial responses + # completed responses)/# eligible patients.

Table 7. Phase II trials of combination regimens containing ifosfamide and an anthracycline: percentage of patients with adverse effects.

Study	Grade 3 or 4 hematological toxicity	G3 or 4 nausea/vomiting	Neurotoxicity	Cardiac toxicity	Renal toxicity	# toxic deaths	
<i>Ifosfamide dose ≤ 7.5 g/m² - no prior chemotherapy</i>							
Comandone, 2000 (17)	Leucopenia (grade 4)	10		5 (lethargy)	NR	NR	0
	Neutropenia	45	7				
	Thrombocytopenia	38					
Chevallier, 1993 (18)	Neutropenia	4	14 ^a	0	11	NR	0
	Thrombocytopenia	0					
Schutte, 1993 (19)	Leukocyte nadir <2.0x10 ⁹ /L	73	41	PN 4 (0.5% ≥G3) C 8 (3% ≥G3)	4 (1% >G2)	3 (2% >G2)	1
	NR		NR	17 (2% severe)	2	NR	1
Elias, 1990 (9)	WBC <500 µL	60					
	Platelets <50 x10 ⁹ /L	48	16	7 (G2/3)	0	2	1
	Febrile neutropenia	59					
	Febrile neutropenia + sepsis	13					
Bokemeyer, 1992 (25)	Febrile granulocytopenia	21	NR	4(G3)	7	4 (G3)	1
Bramwell, 1989 (26)	Febrile neutropenia	32 ^b	8	27 (2% severe)	5 (G1)	2 (mild)	0
Shimizu, 2002 (28) [abstract]	Neutropenia	74					
	Leucopenia	63	0	0	NR	0	0
	Thrombocytopenia	11					
Jager, 1996 (30)	Neutropenic infections	7					
	Febrile neutropenia	2	20	0	0	NR	1
	Leucopenia	63					
<i>Ifosfamide dose ≤ 7.5 g/m² - 6-17% of patients had prior chemotherapy</i>							
Toma, 1993 (20)	Leucopenia	29	7	4 (G2)	9 (G1)	NR	0
	Thrombocytopenia	0					
Cantwell, 1988 (22)	NR		38 ^c (G3)	12 (G NR)	NR	6	1
Mansi, 1988 (23)	Leucopenia	56	14 (G3)	6 (G NR)	20 (G1)	0	1
Gonzalez-Manzano, 1993 (24)	Leucopenia	40					
	Febrile leucopenia	36	56	0	4	8 (mild)	1
	Thrombocytopenia	32					
Wiklund, 1992 (27)	Leucopenia	10					
	Thrombocytopenia	7	64	23	6	0	1
	Sepsis	3					
Levy, 1998 (29) [abstract]	Neutropenia	90					
	Febrile neutropenia	40	7	23 ^d	NR	NR	0
	Thrombocytopenia	30					
<i>Ifosfamide dose >7.5 g/m²</i>							
Frustaci, 1993 (31)	Leucopenia	55					
	Thrombocytopenia (G3)	3	19	NR	NR	NR	0
	Febrile neutropenia	0					

Notes: G – grade, NR - not reported; PN - peripheral neuropathy; C - level of consciousness.

^a Percentage of 101 cycles of treatment^b % of courses^c Number of courses of treatment not patients^d transient encephalopathy.

Non-anthracycline combinations including ifosfamide

Seven trials investigated combination chemotherapy regimens with ifosfamide that did not include an anthracycline (5,32-37). The total dose of ifosfamide ranged from four to 10 g/m².

There was one phase II trial of ifosfamide (2.5 g/m²/day by continuous intravenous [iv] on days 1-3) plus cisplatin (100 mg/m² on day 2) as the second-line therapy for metastatic sarcoma (37). All but one of 38 patients had received doxorubicin as part of their previous chemotherapy. The response rate was 21%, and median survival was 11 months. High rates of grade 3 or 4 adverse effects were reported, including leucopenia in 82% of patients, thrombocytopenia in 29%, anemia in 24%, nephrotoxicity in 8%, neurotoxicity in 8%, and sepsis in 5%.

There were four trials of ifosfamide and etoposide that included patients who had received prior chemotherapy (5,32-34). In the trial reported by Yalçın et al (5), 26 patients with advanced or metastatic STS were entered, and all patients received prior chemotherapy with either cyclophosphamide or doxorubicin-based combination chemotherapy. Seven patients achieved a complete response, and three achieved a partial response, for an objective response rate of 38%. Median time-to-progression was 13.3 months. A total of 108 cycles were administered with the following grade 3 or 4 adverse events reported: neutropenia, 21%; thrombocytopenia, 7%; anemia, 2%; and nausea/vomiting, 8%. In the trial reported in abstract form by Kawai et al (32), all patients had advanced STS, and an unreported number received prior chemotherapy (eight patients received prior anthracycline-containing chemotherapy). Six of 22 patients achieved a partial response, for an objective response rate of 27%. The response rate for patients with prior anthracycline chemotherapy was 25%. Toxicity was not well documented; however, neutropenic fever occurred in 10% of courses. In the trial by Edmonson et al, 32 of 44 had chemotherapy for advanced disease or as adjuvant therapy, 25 with doxorubicin (33). The response rate was 16% overall and 15% among those with prior doxorubicin. Median time to progression was 2.3 months and median survival 9.4 months. There was one case of renal failure. Fifteen of 20 patients in the trial by Blair et al had received previous chemotherapy, with nine having doxorubicin-based chemotherapy for advanced disease (34). Among all 20 patients, the response rate was 10.5%, and median survival was 10 months. Grade 3 and 4 toxicity included neutropenia in 89% of patients, anemia in 22%, fever in 5%, and infection in 11%.

The remaining two trials included only patients without prior chemotherapy (35,36). Saeter et al observed a response rate of 40% with ifosfamide and etoposide as the first-line chemotherapy (35). Papai et al reported a response rate of 46% with ifosfamide, etoposide, and cisplatin (36).

DISCUSSION

Numerous studies (6-9) have documented the activity of ifosfamide in patients with STS. The activity of doxorubicin in metastatic STS has been well described in a previous guideline of the Sarcoma DSG (Practice Guideline #11-1: *Doxorubicin-based Chemotherapy for the Palliative Treatment of Adult Patients with Locally Advanced or Metastatic Soft Tissue Sarcoma*). In this document, we concluded that, despite a low overall response rate (20%) and an almost negligible complete response rate, therapy with single-agent doxorubicin is an acceptable therapeutic choice. However, in patients with metastatic or unresectable STS, progress in defining new treatment strategies has been slow, and therapeutic options remain extremely limited. It is therefore relevant to explore whether combination chemotherapy regimens containing ifosfamide produce an advantage in terms of response rate, time to progression, or survival compared to similar regimens without ifosfamide.

Three RCTs of ifosfamide-containing versus non-ifosfamide-containing chemotherapy have been reported to date (12,13,16). Two of those trials (13,16) reported that the addition of

ifosfamide to either doxorubicin or to a regimen of doxorubicin and DTIC significantly improved the response rate. The trial reported by Antman (16) also reported a significant improvement in overall survival for patients who received doxorubicin and DTIC compared to those patients who received MAID alone. The reason for this cannot be discerned from the trial, although it is possible that histological differences in the trial population could have resulted in subtle imbalances in the treatment arms

A meta-analysis of the three trials has indicated that the addition of ifosfamide to a chemotherapy regimen significantly improved the tumour response rate (RR, 1.52, $p=0.009$) but did not produce a significant difference in one-year survival (RR, 0.98, $p=0.76$). We chose to examine one-year survival as, in the RCTs, the median survival of all treatment arms ranged between 8.4 and 13 months. In addition, in this population, survival at one year may represent an appropriate clinical benchmark.

All three RCTs reported higher rates of adverse events in the regimens that contained ifosfamide. Two of the trials reported that grade 3/4 adverse events were much higher in the ifosfamide arm (13,16). The same trials reported greater rates in grade 3/4 myelosuppression in the ifosfamide arm, with one reporting a statistically significant difference (13). In addition, a higher number of toxic deaths were observed in the ifosfamide-containing arm in the studies reported by Edmonson et al (13) and Antman et al (16).

In addition to RCTs, we also elected to include the results of phase II trials in an attempt to further explore the potential impact of prior therapy or ifosfamide dose on the outcomes of interest. It is not possible to draw any firm conclusions from those studies; however, it is of interest to note that response rates in those studies ranged from 10.5 to 60%, and the dose of ifosfamide ($\leq 7.5 \text{ g/m}^2$ vs. $> 7.5 \text{ g/m}^2$) did not appear to have an impact on this. Similarly, patients who were chemotherapy naïve appeared to have similar response and survival rates compared to trials where patients had received prior chemotherapy. Toxicity in those trials was similar to that observed in the RCTs, although higher doses of ifosfamide appear to be associated with higher rates of neurotoxicity.

CONCLUSIONS

While the available evidence indicates that the addition of ifosfamide may improve tumour response, this does not translate into a survival benefit. The evidence also indicates that treatment-related toxicities are clearly increased with the addition of ifosfamide to doxorubicin-containing regimens. Consequently, the Sarcoma DSG does not recommend the addition of ifosfamide to standard doxorubicin-containing regimens for patients with inoperable, locally advanced or metastatic STS. It is important to note, however, that in patients with inoperable or locally advanced disease, or those with severe symptomatology, tumour response may result in palliation of symptoms or sufficient reduction in size to render an inoperable tumour operable. Therefore, in individual patients, response alone is a valued outcome and under these special circumstances, it may be appropriate to add ifosfamide to a doxorubicin-containing regimen in the first-line setting. In such instances, the dose of ifosfamide should not exceed 7.5 g/m^2 , whether given as a split bolus or continuous infusion program.

ONGOING TRIALS

The Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) was searched for reports of new or ongoing trials. Reports of ongoing trials found from searches performed in MEDLINE, EMBASE, the Cochrane Library, and the conference proceedings of ASCO were also included.

Protocol ID(s)	Title and details of trial
ASCO 2003 Abstract 3316 (38)	Ifosfamide (IFM), doxorubicin (D) and cyclophosphamide (C) chemotherapy for advanced adult soft tissue sarcoma (STS): A Japanese musculoskeletal oncology group (JMOG) study. Outcomes reported: response, toxicity. Patient accrual: 42 patients enrolled.
EORTC-62012	Phase III randomized study of doxorubicin with versus without ifosfamide in patients with locally advanced or metastatic soft tissue sarcoma. Outcomes of interest: survival, response, treatment-related mortality, toxicity. Projected accrual: 450 patients within four years. Summary last modified: 05/2003. Trial status: active. Accessed April 8, 2004. Available at: http://www.cancer.gov/clinicaltrials/view_clinicaltrials.aspx?version=healthprofessional&cdrid=302584&protocolsearchid=860986 .

CONFLICT OF INTEREST

The members of the Sarcoma DSG disclosed potential conflicts of interest relating to the topic of this systematic review. No potential conflicts were declared.

JOURNAL REFERENCE

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For a complete list of Sarcoma Disease Site Group members please visit the CCO website at http://www.cancercare.on.ca/access_PEBC.htm.

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Evidence-based Series # 11-4: Section 3

Ifosfamide-based Combination Chemotherapy in Advanced Soft Tissue Sarcoma: Guideline Development and External Review: Methods and Results

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

Report Date: April 11, 2006

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, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the routine periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-based Series: A New Look to the PEBC Practice Guidelines

Each Evidence-based Series is comprised of the following three sections:

- *Section 1: Clinical Practice Guideline.* This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.

- *Section 2: Systematic Review.* This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.
- *Section 3: Guideline Development and External Review: Methods and Results.* This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed by the Sarcoma DSG of Cancer Care Ontario’s Program in Evidence-based Care (PEBC). The series is a convenient and up-to-date source of the best available evidence on ifosfamide-based combination chemotherapy for patients with inoperable locally advanced or metastatic STS, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Report Approval Panel

Prior to submission of this evidence-based series report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Panel were that the inclusion of the word “routine” in the recommendation created ambiguity in light of the compelling evidence demonstrating lack of benefit and that a rationale for using response as an important and policy-determining outcome was required, as was a rationale for including phase II studies, given the availability of three RCTs. In response, the DSG removed the word “routine”, noted that response is an important outcome in this patient population given their limited treatment options, and noted that the inclusion of phase II studies reflected the previous approach, of including both RCTs and phase II studies, at the time the report was initially started.

External Review by Ontario Clinicians

Following the review and discussion of Sections 1 and 2 of this evidence-based series, the Sarcoma DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.

<p>BOX 1: DRAFT RECOMMENDATIONS (approved for external review February 22, 2006)</p>
<p><i>Target Population</i> Adult patients with inoperable locally advanced or metastatic soft tissue sarcoma.</p>
<p><i>Recommendation</i></p> <ul style="list-style-type: none"> • In patients with metastatic soft tissue sarcoma, the routine addition of ifosfamide to standard doxorubicin containing regimens is not recommended over single agent doxorubicin. However, in patients with symptomatic, locally-advanced, or inoperable soft tissue sarcoma, in whom tumour response might potentially result in reduced symptomatology or render a tumour resectable, it would be reasonable to use ifosfamide in combination with doxorubicin.
<p><i>Qualifying Statements</i></p> <ul style="list-style-type: none"> • In combination with doxorubicin containing regimen, the dose of ifosfamide should not exceed 7.5 g/m² given either as a split bolus or continuous infusion.

Methods

Feedback was obtained through a mailed survey of 74 practitioners in Ontario that included medical oncologists, radiation oncologists, and surgeons. The survey 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 practice guideline. Written comments were invited. The survey was mailed out on February 22, 2006. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Sarcoma DSG reviewed the results of the survey.

Results

Twenty-nine responses were received out of the 74 surveys sent (39% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, nine indicated that the report was relevant to their clinical practice, and they completed the survey. One practitioner was unsure if the guideline was relevant to their practice, and another indicated that the topic was relevant to them but did not complete the questionnaire as they do not work directly with patients. Therefore, the latter practitioner's comments were not included in these results. Key results of the practitioner feedback survey are summarized in Table 1.

Table 1. Responses to eight 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 guideline, as stated in the "Introduction" section of the report, is clear.	8 (100)	0	0
There is a need for a guideline on this topic.	7 (87.5)	1 (12.5)	0
The literature search is relevant and complete.	8 (100)	0	0
The results of the trials described in the report are interpreted according to my understanding of the data.	8 (100)	0	0
The draft recommendations in the report are clear.	7 (87.5)	1 (12.5)	0
I agree with the draft recommendations as stated.	8 (100)	0	0
This report should be approved as a practice guideline.	7 (87.5)	1 (12.5)	0
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
	6 (75)	1 (12.5)	1 (12.5)

Summary of Written Comments

Of the nine respondents, one clinician provided suggestions for future document development and content. This was noted at the PEBC office. One practitioner noted that there was an error in the discussion regarding the presentation of study results.

Modifications/Actions

The error was noted and was corrected in the report.

Funding

The PEBC is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

EVIDENCE-BASED SERIES # 11-4

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For information about the PEBC and the most current version of all reports, please visit the CCO Web site at <http://www.cancercare.on.ca/> or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775

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