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Evidence-based Series 11-5 EDUCATION AND INFORMATION 2011

Dose-intensive Chemotherapy with Growth Factor or Autologous Bone Marrow/Stem Cell Transplant Support in Advanced or Metastatic Adult Soft Tissue Sarcoma

Members of the Sarcoma Disease Site Group

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

Evidence-based Series 11-5 was reviewed in 2011 and put in the Education and Information section by the Sarcoma Disease Site Group (DSG) on May 31, 2011. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).

Evidence-based Series (EBS) 11-5 EDUCATION AND INFORMATION 2011, the resulting review report,
consists of the following 5 parts:

1. **Guideline Report Overview**
2. **Section 1: Clinical Practice Guideline**
3. **Section 2: Systematic Review**
4. **Section 3: Guideline Development and External Review**
5. **Document Assessment and Review Tool**

and is available on the CCO website (http://www.cancercare.on.ca)
PEBC Sarcoma Disease Site Group page at:
http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/sarcoma-ebs/.

Release Date: September 15, 2011

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version Apr 2006	1980 to 2005	Full Report	Peer review publication[1,2] Web publication	Not Applicable
Reviewed version May 2011	Document Assessment and Review Tool		Updated Web publication	Guideline ARCHIVED

[1] Verma S, Younus J, Haynes AE, Stys-Norman D, Blackstein M; Sarcoma Disease Site Group|| of Cancer Care Ontario's Program in Evidence-based Care. Dose-intensive chemotherapy with growth factor or autologous bone marrow or stem-cell transplant support in first-line treatment of advanced or metastatic adult soft tissue sarcoma: a clinical practice guideline. Curr Oncol. 2008;15(2):31-5.

[2] Verma S, Younus J, Stys-Norman D, Haynes AE, Blackstein M; Sarcoma Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Dose-intensive chemotherapy with growth factor or autologous bone marrow/stem cell transplant support in first-line treatment of advanced or metastatic adult soft tissue sarcoma. Cancer. 2008 Mar 15;112(6):1197-205" doi:I 10.1002/cncr.23302.

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Evidence-based Series 11-5 ARCHIVED 2011

Dose-intensive Chemotherapy with Growth Factor or Autologous Bone Marrow/Stem Cell Transplant Support in Advanced or Metastatic Adult Soft Tissue Sarcoma

Guideline Review Summary

Review Date: May 31, 2011

The 2006 guideline recommendations are

ARCHIVED

This means that the recommendations will no longer be maintained but may still be useful for academic or other informational purposes.

OVERVIEW

Evidence-based Series History

This guidance document was originally released by the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO), in 2006. In May 2011, the PEBC guideline update strategy was applied, and the recommendations were archived.

Update Strategy

The PEBC update strategy includes an updated search of the literature, the review and interpretation of new eligible evidence by the clinical experts from the authoring panel and consideration of the guideline and its recommendations based on the new available evidence. See the Document Assessment and Review Tool at the end of this EBS.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

1. In patients with inoperable locally advanced or metastatic soft tissue sarcoma, does first line dose-intensive chemotherapy supported by growth factor or autologous bone marrow/stem cell transplantation improve response rate, time-to-disease progression, or survival compared with standard dose chemotherapy?
2. What are the effects of first line dose-intensive chemotherapy supported by growth factor or autologous bone marrow/stem cell transplantation on toxicity and quality of life?

Literature Search and New Evidence

A search for new literature with respect to this question was not conducted since it was determined that the recommendations regarding these questions are no longer relevant. The guideline and its recommendations have been ARCHIVED.

Impact on Guidelines and Its Recommendations

The Sarcoma DSG **ARCHIVED** the 2006 recommendations. Therefore this guideline will no longer be updated.

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Evidence-Based Series #11-5: Section 1

Dose-intensive Chemotherapy with Growth Factor or Autologous Bone Marrow/Stem Cell Transplant Support in the First-line Treatment of Advanced or Metastatic Adult Soft Tissue Sarcoma: A Clinical Practice Guideline

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

Please see the EBS 11-5 Archived 2011 Guideline Review Summary and the Document Assessment and Review Tool for the summary of updated evidence published between 2005 and 2011.

Report Date: April 11, 2006

Questions

1. In patients with inoperable locally advanced or metastatic soft tissue sarcoma, does first-line dose-intensive chemotherapy supported by growth factor or autologous bone marrow/stem cell transplantation improve response rate, time-to-disease progression, or survival, compared with standard-dose chemotherapy?
2. What are the effects of first line dose-intensive chemotherapy supported by growth factor or autologous bone marrow/stem cell transplantation on toxicity and quality of life?

For the purposes of this practice guideline, "dose-intensive chemotherapy" is defined as regimens administered with the intent to increase standard doses of chemotherapy, supported by the use of hematopoietic growth factors and/or autologous bone marrow/stem cell transplant support. Standard chemotherapy includes regimens that have been previously evaluated in a large phase II trial or a randomized phase III trial without growth-factor support.

Recommendations

- Dose-intensive chemotherapy with growth factor support is not recommended in the first-line treatment of patients with inoperable locally advanced or metastatic soft tissue sarcoma.

- There is insufficient data to support the use of high-dose chemotherapy with autologous bone marrow/stem cell transplantation as first-line treatment in this group of patients.
- Eligible patients should be encouraged to enter clinical trials assessing novel approaches or compounds.

Qualifying Statements

- High-dose chemotherapy with growth factor or autologous bone marrow/stem cell transplantation and standard-dose chemotherapy have similar adverse effects. The incidence of grade 3/4 thrombocytopenia is significantly higher; neutropenic fever and febrile neutropenia occur more frequently with high-dose regimens. Compared to standard treatment, the rate of treatment related deaths is also higher with high-dose regimens.

Key Evidence

- Evidence is available from two phase III randomized trials, one phase II randomized trial, 11 phase II trials, and five phase I dose-escalation trials.
- One randomized trial (N=314) did not detect significant differences in response rate (p=0.65) or survival (log-rank p=0.98) between high-dose doxorubicin (75 mg/m^2) plus ifosfamide (5 g/m^2) with granulocyte-macrophage colony stimulating factor (GM-CSF) and doxorubicin (50 mg/m^2) plus ifosfamide (5 g/m^2) at standard doses. Progression-free survival, however, was significantly longer in the high-dose arm (log-rank p=0.03). There were higher rates of thrombocytopenia, infection, grade 3/4 asthenia, and grade 3/4 stomatitis with high-dose chemotherapy compared to standard-dose chemotherapy.
- Preliminary results from a second randomized trial (N=162), reported only in abstract form, indicate no benefit with respect to tumour response for an intensified MAID (mesna, Adriamycin [doxorubicin] 75 mg/m^2, ifosfamide 9 g/m^2, and dacarbazine 1200 mg/m^2) regimen with granulocyte-colony stimulating factor (G-CSF) support compared to standard MAID (doxorubicin 60 mg/m^2, ifosfamide 7.5 g/m^2, and dacarbazine [DTIC] 900 mg/m^2). Survival data have not yet been reported for that trial. The rate of grade 4 thrombocytopenia was significantly higher with the high-dose regimen.
- Four phase II trials of high-dose regimens that contained ifosfamide (>7.5 g/m^2/per cycle) and an anthracycline observed tumour response rates in excess of 50%.
- Dose-liming toxicity for the dose-intensive chemotherapy regimens evaluated in phase I trials included neutropenia, thrombocytopenia, mucositis, neutropenic fever, vomiting, fatigue, and nephrotoxicity.

Future Research

Future research in patients with inoperable, locally advanced, or metastatic soft tissue sarcoma should focus on the identification of novel compounds or combinations that improve the response rate or survival of those patients. If high-dose chemotherapy with growth factor support or autologous bone marrow/stem cell transplantation is to be pursued, potentially myeloablative combinations similar to those used in hematological malignancies should be compared to conventional approaches. Outcomes should include survival, response, response duration, symptom control, and 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].

- Draft Practice Guideline Report #11-4: *Ifosfamide-based Combination Chemotherapy in Advanced Soft Tissue Sarcoma* [guideline under development].

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Evidence-Based Series #11-5: Section 2

Dose-intensive Chemotherapy with Growth Factor or Autologous Bone Marrow/Stem Cell Transplant Support in the First-line Treatment of Advanced or Metastatic Adult 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)

Please see the EBS 11-5 Archived 2011 Guideline Review Summary and the Document Assessment and Review Tool for the summary of updated evidence published between 2005 and 2011.

Report Date: April 11, 2006

QUESTIONS

1. In patients with inoperable locally advanced or metastatic soft tissue sarcoma (STS), does first line dose-intensive chemotherapy supported by growth factor or autologous bone marrow/stem cell transplantation improve response rate, time-to-disease progression, or survival compared with standard dose chemotherapy?
2. What are the effects of first line dose-intensive chemotherapy supported by growth factor or autologous bone marrow/stem cell transplantation on toxicity and quality of life?

For the purposes of this practice guideline, "dose-intensive chemotherapy" is defined as regimens administered with the intent to increase standard doses of chemotherapy supported by the use of hematopoietic growth factors and/or autologous bone marrow/stem cell transplant support. Standard chemotherapy includes regimens that have been previously evaluated in a large phase II trial or a randomized phase III trial without growth factor support.

INTRODUCTION

The treatment of advanced or metastatic STS is one of the most challenging areas in oncology. While the multidisciplinary management of early-stage localized disease has led to

a number of improved outcomes, therapy for inoperable advanced or metastatic disease remains problematic. In patients with STS who develop metastases, the lung is the most common site and, in many patients, may be the only site of distant dissemination (1). Although surgical resection of pulmonary metastases may be curative in 15% to 30% of patients with isolated slow-growing metastases, the majority of patients with metastatic STS are not candidates for surgical resection (2,3). Patients with metastatic involvement have a median survival of approximately one year, and, for most of these patients, systemic therapy is the only therapeutic option. It is widely acknowledged that the cytotoxic agents doxorubicin and ifosfamide have the highest activity in metastatic STS, with approximately 20-30% of patients responding to these drugs as single agents (4-7). Improved response rates have been observed with combination chemotherapy involving doxorubicin and ifosfamide at conventional doses (8); however, when data from randomized trials comparing single-agent doxorubicin to doxorubicin-based combination chemotherapy were pooled in a recent meta-analysis, response and survival outcomes were not significantly different for single-agent doxorubicin versus combination therapy (4).

More recent efforts to improve response rate—and by inference, disease-free survival and overall survival—have involved the exploration of dose-intensive chemotherapy regimens incorporating growth factors and/or autologous cellular support. Dose-response relationships have been observed for both doxorubicin and ifosfamide as single agents in STS (8-12). A number of prospective trials have demonstrated that growth factors, such as granulocyte-colony stimulating factor (G-CSF) and granulocyte macrophage-colony stimulating factor (GM-CSF), or autologous bone marrow/stem cell transplantation may improve the hematologic tolerance of dose-intense combination-chemotherapy regimens (13-15).

Thus far, the literature dealing with the subject of dose-intensive chemotherapy in adult STS is sparse, and the majority of studies are non-randomized trials involving small numbers of subjects. However, as the therapeutic options for adult patients with advanced or metastatic STS are extremely limited and the possibility of a cure for these patients is virtually nonexistent, the Sarcoma Disease Site Group (DSG) elected to systematically review the available evidence on dose-intensive chemotherapy for adult patients with locally advanced or metastatic STS and to subsequently develop a clinical practice guideline based on that evidence.

METHODS

This systematic review was developed by CCO's PEBC, using the methods of the Practice Guidelines Development Cycle (16). Evidence was selected and reviewed by two members of the PEBC Sarcoma DSG and methodologists.

This systematic review is a convenient and up-to-date source of the best available evidence on dose-intensive 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 (1982 to January Week 4, 2005), EMBASE (1980 to February Week 6, 2005), and the Cochrane Library (2005, Issue 1) databases were searched. Disease-specific search terms "sarcoma" (Medical subject heading [MeSH]), "soft tissue neoplasms" (MeSH), "*sarcoma/dt" (exploded MeSH term) and "soft tissue sarcoma" (text word) were combined with treatment-specific terms "drug therapy" (MeSH), "drug therapy, combined" (MeSH),

"granulocyte-macrophage colony-stimulating factor" (MeSH), "granulocyte colony-stimulating factor" (MeSH), "bone marrow transplantation" (MeSH), "transplantation, autologous" (MeSH), "hematopoietic stem cell transplantation" (MeSH) and each of the following phrases used as text words: "chemotherapy", "high-dose", "dose-intense", "g-csf", "gm-csf", "growth factor", "abmt", "pbsc", "psct", "transplant". These terms were combined with search terms for the following publications types: practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, phase I clinical trials, phase II clinical trials, and phase III clinical trials.

In addition, the 1998-2004 conference proceedings of the American Society of Clinical Oncology (ASCO) 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 two reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

Study Selection Criteria

Inclusion Criteria

Articles (full reports or abstracts) were eligible for inclusion in this systematic review of the evidence if they matched one of the following sets of criteria:

1. They were first line randomized controlled trials (RCTs) comparing dose-intensive chemotherapy regimens, supported by growth factor (e.g., G-CSF or GM-CSF) or autologous bone marrow/stem transplantation, with a lower- or standard-dose chemotherapy regimen in adult patients with locally advanced or metastatic STS. They reported data, by allocation group, on overall survival, time-to-progression, or tumour response rate.

   "Dose-intensive chemotherapy" was defined as regimens for which the investigators expressed intent to increase standard doses of chemotherapy supported by the use of hemopoietic growth factors and/or autologous bone marrow/stem cell transplant support. Comparator regimens were accepted as standard chemotherapy if they had been previously evaluated in a large phase II trial or a randomized phase III trial without growth-factor support.
2. First-line single-arm non-comparative trials were also included if they were phase II trials that reported toxicity data, response rates, or survival rates or if they were phase I trials that reported dose-limiting toxicity (DLT) or maximum tolerable dose (MTD) for adult patients who received dose-intensive chemotherapy (as defined above) as first-line therapy for locally advanced or metastatic STS. The rationale for including the non-comparative trials was due to the paucity of RCTs and to permit as detailed a description as possible of the potential efficacy and toxicity of dose-intensive chemotherapy in STS.

Exclusion Criteria

Articles were excluded from the systematic review if:

1. They included patients with pediatric sarcomas, bone sarcoma, or small round cell sarcomas including Ewing's sarcoma.
2. They assessed dose-intensive chemotherapy in the second-line setting.
3. They were letters or editorials.
4. They were published in a language other than English.

Synthesizing the Evidence

The DSG considered pooling data from relevant randomized trials but decided that meta-analysis would not be appropriate because the two phase III trials found by the literature search evaluated different chemotherapy regimens.

RESULTS

Literature Search Results

A total of 19 reports evaluating dose-intensive chemotherapy in adult patients with locally advanced or metastatic STS were identified by the literature search and included in this systematic review of the evidence (Table 1). Those included two phase III randomized trials (17,18), twelve phase II trials (three abstract and nine completed trials) (13,19-29), and five phase I dose-escalation trials (30-34).

Table 1. Clinical trials of dose-intensive first-line chemotherapy included in this systematic review of the evidence.

Dose-intensive chemotherapy regimen, control treatments for randomized trials*	Trial Author, Year, (Ref)	Number enrolled
Phase III		
doxorubicin 75 mg/m^2 + ifosfamide 5 g/m^2 + GM-CSF vs. doxorubicin 50 mg/m^2 + ifosfamide 5 g/m^2	Le Cesne, 2000 (17)	314
MAID+25% (doxorubicin 75 mg/m^2 + ifosfamide 9 g/m^2 + DTIC 1200 mg/m^2) + G-CSF vs. MAID (doxorubicin 60 mg/m^2 + ifosfamide 7.5 g/m^2 + DTIC 900 mg/m^2)	Bui, 1998 (18) [abstract]	162
Phase II		
doxorubicin 75 mg/m^2 + ifosfamide 5 g/m^2 + GM-CSF	Steward, 1993 (13)	111
doxorubicin 75 mg/m^2 + ifosfamide 10 g/m^2 + G-CSF	Patel, 1997 (19) [abstract]	79
doxorubicin 20 mg/m^2 + ifosfamide 12.5 g/m^2 + G-CSF	De Pas, 1998 (20)	14
doxorubicin 90 mg/m^2 + ifosfamide 12.5 g/m^2 + G-CSF	Maurel, 2004 (21)	60
doxorubicin 60 mg/m^2 + ifosfamide 6 g/m^2 + G-CSF vs. doxorubicin 60 mg/m^2 + ifosfamide 12 g/m^2 + G-CSF	Worden, 2003 (22) - randomized trial	86
doxorubicin 50 mg/m^2 + ifosfamide 10 g/m^2 + DTIC 1250 mg/m^2 + G-CSF	Lin, 1999 (23)	35
Induction: doxorubicin 75 mg/m^2 + ifosfamide 6 g/m^2 + G-CSF; then PBSCR Followed by: ifosfamide 12 g/m^2 + etoposide 1.2 g/m^2 + carboplatin 1.2 g/m^2	Schlemmer, 2004 (24) [abstract]	55
liposomal daunorubicin 100 mg/m^2 + ifosfamide 5 g/m^2 + G-CSF	Deckert, 2004 (25) [abstract]	40
epirubicin 90 mg/m^2 + ifosfamide 12.5 g/m^2 + G-CSF	Reichardt, 1998 (26)	46
epirubicin 110 mg/m^2 + ifosfamide 10 g/m^2 + G-CSF	Palumbo, 1999 (27)	39
etoposide (escalating 600-840 mg/m^2) + ifosfamide (escalating 4.5-6.3 g/m^2) + PBSCR + G-CSF	Saeter, 1997 (28)	107
ifosfamide 14 g/m^2 + GM-CSF	Buesa, 1998 (29)	48
Phase I		
epirubicin (escalating 100-140 mg/m^2) + ifosfamide (fixed 9 g/m^2) + GM-CSF	Frustaci, 1997 (30)	38

Dose-intensive chemotherapy regimen, control treatments for randomized trials*	Trial Author, Year, (Ref)	Number enrolled
epirubicin (fixed 120 mg/m^2) + ifosfamide (escalating 9-12 g/m^2) + G-CSF	Frustaci, 1999 (31)	31
doxorubicin (fixed 75 mg/m^2) + ifosfamide (escalating 8-15 g/m^2) + G-CSF	De Pas, 2002 (32)	35
doxorubicin (fixed 75 mg/m^2) + ifosfamide (escalating 8-16 g/m^2) + G-CSF + PBSCR	Bokemeyer, 1997 (33)	18
escalating MAID (+25% to +100%) + G-CSF	Chevreau, 1999 (34)	16

Notes: DTIC – dacarbazine, G-CSF – granulocyte colony stimulating factor, GM-CSF – granulocyte macrophage-colony stimulating factor, MAID – mesna-Adriamycin (doxorubicin)-ifosfamide-dacarbazine, PBSCR – peripheral blood stem cell rescue, vs. – versus.
* mesna given with ifosfamide.

All but two trials (28,29) administered chemotherapy that included both an anthracycline (doxorubicin, epirubicin, or liposomal daunorubicin) and ifosfamide. Sixteen trials (13,17-23,25-27,29-32,34) used hematopoietic growth factors, alone, and three trials used G-CSF plus peripheral-blood stem cell rescue (24,28,33). Five small non-comparative trials of high-dose chemotherapy with peripheral stem cell transplantation did not meet the eligibility criteria for this guideline because they included patients with bone sarcomas (35-37) or patients receiving second-line chemotherapy (38,39).

Outcomes

Randomized trials

Two randomized trials compared standard to higher doses of chemotherapy (17,18). Both trials incorporated a colony-stimulating factor into the high-dose treatment regimen. A full discussion of those studies is hindered by the fact that one of the trials is reported in abstract form only (18). Patients who had received prior chemotherapy were excluded from both trials. Neither trial was double blind, and no published information is available on the concealment of allocation prior to randomization. The published report of a trial by Le Cesne et al included a justification of sample size, which was achieved (17). Data on survival, tumour response, and disease progression are summarized in Table 2. No quality-of-life data have been published for those trials. Toxicity data appear later in the guideline report under the subtitle Adverse Effects.

In a trial conducted by the European Organization for Research and Treatment of Cancer (EORTC), Le Cesne et al randomized 314 patients to receive either a standard dose of doxorubicin and ifosfamide or a high dose of doxorubicin combined with a standard dose of ifosfamide (17). The patients randomized to the high-dose regimen received GM-CSF. Six percent of randomized patients were excluded from the analysis because they did not meet the eligibility criteria for the trial. There were no significant differences between treatments in response rate (p=0.65) or survival (log-rank p=0.98). Progression-free survival, however, was significantly longer in the high-dose arm (log-rank p=0.03); one-year progression-free survival rates were 20% with standard chemotherapy and 28% with high-dose chemotherapy.

In the study by Bui et al, patients were randomized to receive either standard dose MAID (mesna, Adriamycin [doxorubicin], ifosfamide, and dacarbazine) or MAID+25% with G-CSF support (18). Preliminary results of that study, reported thus far only in abstract form, suggest no benefit for the intensified regimen in terms of tumour response. Survival data have not yet been reported.

Table 2. Randomized trials of dose-intensive chemotherapy: clinical outcomes.

Study Author, Year (Ref)	Treatment groups	# pts entered # pts eligible # pts evaluable	Median survival (months)	Median time to progression (months)	Response rate* (CR+PR)
Le Cesne, 2000 (17)	doxorubicin 50 mg/m^2 ifosfamide 5 g/m^2 (+ mesna)	157 149 147	13	4.4	21%
	doxorubicin 75 mg/m^2 ifosfamide 5 g/m^2 GM-CSF (+ mesna)	157 145 133	13	6.7	23%
Bui, 1998 (18) [abstract]	MAID[a]	80 NR 76	NR	NR	37%
	MAID+25%[b] +G-CSF	82 NR 72	NR	NR	43%

Notes: CR – complete response, G-CSF – granulocyte colony stimulating factor, GM-CSF – granulocyte macrophage-colony stimulating factor, MAID – mesna-Adriamycin (doxorubicin)-ifosfamide-dacarbazine, NR – not reported, PR – partial response, pts – patients, Ref – reference.

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

[a] doxorubicin 60 mg/m^2, ifosfamide 7.5 g/m^2, DTIC 900 mg/m^2.

[b] doxorubicin 75 mg/m^2, ifosfamide 9 g/m^2, DTIC 1200 mg/m^2.

Phase II Trials

Twelve phase II trials (13,19-29) investigated dose-intensive chemotherapy in patients with STS. The abstract by Patel et al, prepared for the 1997 meeting of the Connective Tissue Oncology Society, reported on a group of 79 patients who participated in one of three sequential trials (19). This report included a smaller proportion of patients with metastatic disease (53%), as opposed to primary sarcoma, than did most other trials listed in Table 3. One phase II trial, by De Pas et al, contributed data on only 14 patients (20).

In seven of the 11 single-arm phase II trials summarized in Table 3, ifosfamide and an anthracycline were administered in combinations in which one or both drugs were given at higher than standard doses with G-CSF or GM-CSF (13,19,21,24-27). Four trials used doxorubicin (75-90 mg/m^2 per cycle) (13,19,21,24), and two used epirubicin (90-110 mg/m^2 per cycle) (26,27), one trial used liposomal daunorubicin (100 mg/m^2 per cycle) (25), and one phase II dose-escalation trial examined etoposide and ifosfamide (600 mg/m^2 and 4.5 g/m^2, respectively, with a 10% increase in dose per course) (28). Response rates ranged from 36% to 63% in nine trials of an anthracycline combined with ifosfamide at doses >7.5 g/m^2/cycle and median survivals ranging from 13 months to 24 months (19,21,23-27).

Patel et al included a subset of patients with primary STS of extremity origin, in whom the objective response rate was 80%; 52% of patients with metastatic disease responded (19). Steward et al (13), used a similar regimen to the high-dose arm in the randomized trial by Le Cesne et al described above (17) but observed a higher response rate than that seen in the RCT. In the phase II dose-escalation trial reported by Saeter et al (28), no significant correlation was found between tumour response and mean dose level (Spearman coefficient 0.129, p=0.24). The trial by Buesa et al (29) differed from the other phase II trials in two ways. That study investigated dose-intensive single-agent ifosfamide, and GM-CSF was administered only to patients who experienced one episode of neutropenic fever or had no hematologic recovery by day 28. Sixty percent of patients received GM-CSF.

One randomized phase II trial reported by Worden et al (22) was identified, in addition to the single-arm studies summarized in Table 3. Eighty-six patients were enrolled, 82 were randomized, and 79 were evaluated in that study comparing standard-dose ifosfamide (6 g/m^2) or high-dose ifosfamide (12 g/m^2), both given in combination with doxorubicin (60 mg/m^2) and G-CSF. Patients were stratified for localized (n=52) versus metastatic disease (N=27) prior to randomization. Two- and three-year overall survival rates were higher for the standard-dose arm than for the high-dose arm (73% versus [vs.] 57% and 52% vs. 49%, respectively). Statistical significance was not reached in those differences (relative hazard ratio [HR] of death for the high-dose arm compared to the standard-dose arm was 1.39, 95% confidence interval [CI], 0.70 to 2.77, p=0.34). One-year disease-free survival was 55% for the high-dose arm and 52% for the standard-dose arm (HR 1.08, 95% CI, 0.56 to 2.09, p=0.81).

Among 27 patients with metastatic disease, two-year overall survival was 46% for both the high-dose and standard-dose arms (HR 1.18, 95% CI, 0.44 to 3.14). However, the one-year disease-free survival rate for that group of patients was higher for the high-dose arm (29%) than for the standard-dose arm (15%). Among 52 patients with localized disease, two-year overall survival was 64% for the high-dose arm and 88% for the standard-dose arm (HR 1.64, 95% CI, 0.62 to 4.31). One-year disease-free survival was 65% for the high-dose arm and 75% for the standard-dose arm.

Table 3. Single-arm phase II trials of dose-intensive chemotherapy.

Study Author, Year (Ref)	# pts entered # pts eligible # pts evaluable	Dose-intensive regimen (+mesna)		Growth factor (daily dose)	Median survival (months)	Response Rate[a] (CR+PR)
Steward, 1993 (13)	111 104 104	doxorubicin ifosfamide	75 mg/m^2 5 g/m^2 every 3 weeks	GM-CSF 250 µg/m^2 d2-15	15	45%
Patel, 1997 (19) [abstract]	NR NR 79	doxorubicin ifosfamide	75-90 mg/m^2 10 g/m^2 every 3 weeks	G-CSF 5 µg/kg from d5	NR	63%
De Pas, 1998 (20)	14 14 14	doxorubicin ifosfamide	20 mg/m^2/d, d1-3 2.5 g/m^2/d, d1-5 every 3 weeks	G-CSF 5 µg/kg d7-14	NR	50%
Maurel, 2004 (21)	60 57 53	doxorubicin ifosfamide	30 mg/m^2/d, d1-3 every 2 weeks 12.5 g/m^2, over 5d every 3 weeks x 3[b]	G-CSF 5 µg/kg d4-13[c]	13	38%[d]
Lin, 1999 (23)	39 35 35	doxorubicin ifosfamide DTIC	50mg/m^2, d1 2 g/m^2/d, d1-5 250 mg/m^2/d, d1-5 every 3 weeks	G-CSF 2 µg /kg d6-19	15	46%
Schlemmer, 2004 (24) [abstract]	55 55 55	doxorubicin ifosfamide followed by: ifosfamide etoposide carboplatin	75 mg/m^2 x6 6 g/m^2 12 g/m^2 NR 1.2 mg/m^2 1.2 mg/m^2	G-CSF dose NR PBSCR[e]	23	36%
Deckert, 2004 (25) [abstract]	40 35 29	liposomal-daunorubicin ifosfamide	100 mg/m^2 5 g/m^2, over 24 hours every 4 weeks	G-CSF dose NR	16	31%
Reichardt, 1998 (26)	46 46 46	epirubicin ifosfamide	45 mg/m^2/d, d2,3 2.5 g/m^2/d, d1-5 every 3 weeks	G-CSF 5 µg/kg d6-15	24	52%
Palumbo, 1999 (27)	39 39 39	epirubicin ifosfamide	55 mg/m^2/d, d1,2 2.5 g/m^2/d, d1-4 every 3 weeks	G-CSF 200 µg d6-12	19	59%
Saeter, 1997 (28)	107 92 86	etoposide[f] ifosfamide[f]	600 mg/m^2, over 3d 1.5 g/m^2/d, d1-3 every 3 weeks	G-CSF 5 µg/kg d4-15	19	41%
Buesa, 1998 (29)	48 47 45	ifosfamide	14 g/m^2 over 6d every 4 weeks	GM-CSF[g] 5 µg/kg d7-16	19	38%

Notes: CR – complete response, stimulating factor, d – day(s), DTIC – dacarbazine, G-CSF – granulocyte colony GM-CSF – granulocyte macrophage colony stimulating factor, NR – not reported, PBSCR – peripheral blood stem cell rescue, PR – partial response, pts – patients, Ref – reference.

[a] (# partial responses + # complete responses) /# evaluable patients.

[b] ifosfamide administration began two weeks after the third doxorubicin cycle.

[c] G-CSF was given 24 hours after doxorubicin.

[d] response rate calculated after completion of entire therapy (doxorubicin and ifosfamide).

[e] peripheral blood stem cells were collected after 4 cycles of doxorubicin/ifosfamide.

[f] doses for each drug were increased 10% in the next course up to a maximum of 140% of the baseline dose if patient had adequate hematological activity.

[g] to 60% of patients.

Dose Escalation (Phase I) Trials

Five phase I trials of dose-intensive chemotherapy with ifosfamide and an anthracycline are summarized in Table 4 (30-34). Those studies were designed to determine the MTD of epirubicin given with a fixed dose of ifosfamide (30), ifosfamide given as a continuous infusion with a fixed dose of an anthracycline (31-33), or increasing doses for the MAID regimen (34). MTD was the dose at which a substantial number of patients suffered dose-limiting toxicity. At the MTD, dose reductions were required because of serious hematologic toxicity, mucositis, neutropenic fever, vomiting and fatigue, and nephrotoxicity, which were observed in all the trials (30-34). Although not a primary study objective, tumour response was also reported.

Table 4. Phase I trials of dose-intensive chemotherapy.

Study Author, Year (Ref)	**Treatment**	**# entered** **# evaluable**	**Maximum tolerated dose**	**Response Rate* (CR+PR)**
Frustaci, 1997 (30)	three doses of epirubicin: 50, 60, 70 mg/m^2/day, 2 d ifosfamide 1.8 g/m^2/day, 5 d GM-CSF 5 µg/kg/d	38 37	epirubicin 70 mg/m^2/d with ifosfamide 1.8 g/m^2/d	54%
Frustaci, 1999 (31)	two doses of ifosfamide: 9 g/m^2 (72 hr), 10.5 g/m^2 (84 hr) epirubicin 60 mg/m^2/day, 2 d G-CSF 300 µg/d	31 25	ifosfamide 10.5 g/m^2 with epirubicin 60 g/m^2/d	28%
De Pas, 2002 (32)	six doses of ifosfamide: 8, 9, 10, 12, 13, 15 g/m^2 , continuous infusion, d 1-12 doxorubicin 75 mg/m^2, d 8 G-CSF 300 µg/d	35 30	ifosfamide 15 g/m^2 with doxorubicin 75 mg/m^2	53%
Bokemeyer, 1997 (33)	five doses of ifosfamide: 8, 10, 12, 14, 16 g/m^2, continuous infusion, d 1-4 doxorubicin 75 mg/m^2, d 1 G-CSF 5 µg/kg/d peripheral blood stem cells	18 15	ifosfamide 16 g/m^2 with doxorubicin 75 mg/m^2	50%
Chevreau, 1999 (34)	Six MAID regimens: standard, +25%, +45%, +65%, +85%, +100%, d 1-3 two doses of G-CSF: 5 or 10 µg/kg/d	16 15	MAID+45%: doxorubicin 30 mg/m^2/d dacarbazine 500 mg/m^2/d ifosfamide 3 g/m^2/d	53%

Notes: d – day(s), CR – complete response, stimulating factor, G-CSF – granulocyte colony stimulating factor, GM-CSF – granulocyte macrophage colony stimulating factor, MAID – mesna-Adriamycin (doxorubicin)-ifosfamide-dacarbazine, PR – partial response, Ref – reference.

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

Adverse Effects

Toxicity data, summarized in Table 5, was available for both phase III trials (17,18) and all phase II trials (13,19-29).

The randomized trial by Le Cesne et al (17) observed a higher rate of thrombocytopenia with high-dose chemotherapy compared to standard-dose, but no p-value was reported. More patients receiving the high-dose regimen experienced infections compared to those receiving standard-dose chemotherapy (16.6% vs. 4.6%; p=0.0004). There were two toxicity-related deaths due to kidney failure and septic shock in the high-dose arm and one death due to septic shock in the standard-dose arm. The incidence of grade 3/4 asthenia was significantly higher in the high dose arm (16% vs. 4.5%; p=0.0005), as was grade 3/4 stomatitis (13% vs. 4%; p=0.008).

Important differences between regimens in the incidence of adverse events were observed in the randomized trial by Bui et al (18). There were five toxicity-related deaths in the MAID+25% arm, but causes of death were not reported in the abstract. The rate of grade 4 thrombocytopenia was significantly higher with intensified MAID, compared with standard-dose MAID (p=0.0001). The incidence of febrile neutropenia was higher with MAID+25%, but the difference was not statistically significant (66% vs. 54% with standard-dose MAID).

Experience in the phase II trials was similar. As might be expected, hematologic toxicity including thrombocytopenia and neutropenia, was commonly observed. In addition, febrile neutropenic rates ranged between 14% and 35% (13,20,21,26). Despite this, it is of interest that only four treatment-related deaths among 585 participants were reported (13,19,29).

Table 5. Clinical trials of dose-intensive chemotherapy: Percentage of patients with adverse effects.

Study Author, Year (Ref)	Chemotherapy Regimen (+ mesna)	Grade 3/4 hematological toxicity		Grade 3/4 nausea/ vomiting	Neuro-toxicity	Cardiac toxicity	Renal toxicity	# toxic deaths
Phase III trials								
Le Cesne, 2000 (17)	dox ifos	neutropenia thrombocytopenia	92 8	10	NR	1 (G2/3)	NR	1
	dox ifos GM-CSF	neutropenia thrombocytopenia	90 50	13	NR	2 (G2/3)	NR	2
Bui, 1998 (18) [abstract]	MAID	thrombocytopenia[a](G4)	21	NR	NR	NR	NR	0
	MAID+25% G-CSF	thrombocytopenia[a](G4)	64	NR	NR	NR	NR	5
Phase II trials								
Steward, 1993 (13)	dox+ ifos GM-CSF	NR		30 (G3)	0	3 (1 G4, 2 G1/2)	1 (G2)	2
Patel, 1997 (19) [abstract]	dox + ifos G-CSF	NR		14	NR	1 (G4)	NR	1
De Pas, 1998 (20)	dox + ifos G-CSF	neutropenia thrombocytopenia	87 39	0	4 (G4)	NR	0	0
Maurel, 2004 (21)	dox + ifos[b] G-CSF	neutropenia thrombocytopenia anemia[c] anemia[d]	46 24 13[c] 28[d]	9[c] 14[d] (G3/4)	0[c] 8[d] (G3/4)	2[c] 0[d] (G2)	0	0
Worden, 2005 (22)	dox ifos G-CSF	anemia leukopenia neutropenia thrombocytopenia	23 49 49 15	NR	0 (G3/4)	NR	5 (<20mL/min)	0
	dox ifos G-CSF	anemia leukopenia neutropenia thrombocytopenia	58 88 88 63	NR	10 (G3/4)	NR	3 (<20mL/min)	5[g]
Lin, 1999 (23)	dox + ifos + DTIC G-CSF	platelets	6	14	NR	NR	NR	0
Schlemmer, 2004 (24) [abstract]	dox + ifos + G-CSF; then PBSCR followed by: ifos + etop + carbo	G4 hematological toxicity	38	NR	NR	NR	NR	0
Deckert, 2004 (25) [abstract]	l-daun + ifos G-CSF	neutropenic fever	9[e]	0	4.8[e] (G2)	0	3 (1 pt)	NR
Reichardt, 1998 (26)	epi + ifos G-CSF	leukopenia thrombocytopenia neutropenic fever	100 50 37	NR	20 (9% G3/4)	2 (reversible arrhythmia)	17 (G1/2)	0
Palumbo, 1999 (27)	epi + ifos G-CSF	leukoneutropenia thrombocytopenia	33 0	13	0	3 (G1)	13 (G1)	0
Saeter, 1997 (28)	etop[f] + ifos[f] G-CSF	leukopenia thrombocytopenia neutropenic fever	67 33 19	NR	1	NR	0	0
Buesa, 1998 (29)	ifos GM-CSF	leucopenia (G4) thrombocytopenia (G4) neutropenic fever	76 17 48	30	33 (G3)	NR	60 (G1)	1

Notes: carbo – carboplatin, dox – doxorubicin, DTIC – dacarbazine, epi – epirubicin, etop – etoposide, G – grade, G-CSF – granulocyte-colony stimulating factor, GM-CSF – granulocyte macrophage-colony stimulating factor, ifos – ifosfamide, l-daun – liposomal daunorubicin, MAID – mesna-Adriamycin (doxorubicin)-ifosfamide-dacarbazine, NR – not reported, PBSCR – peripheral blood stem cell rescue.

[a] Difference between MAID compared to MAID+25% is statistically significant, $p<0.0001$.

[b] Ifosfamide was administered two weeks after the last cycle of doxorubicin.

[c] For 57 patients that received doxorubicin.

[d] For 47 patients that received ifosfamide.

[e] Percent of 115 cycles administered.

[f] Patients received escalating doses (+10% per course) of etoposide and ifosfamide.

[g] These were early deaths.

DISCUSSION

To date, in patients with metastatic or unresectable soft tissue sarcoma, only two RCTs have been conducted to determine if dose-intensive chemotherapy with growth factor support or autologous bone marrow/stem cell transplantation improves survival, response or time-to-progression, compared to standard-dose chemotherapy in the first-line treatment setting. Only one RCT of 314 patients reported data on all three outcomes of interest, with no significant differences in overall survival or response rate between the two treatment groups (17). One-year progression-free survival was significantly longer in the high-dose chemotherapy arm compared to the standard-dose chemotherapy arm (28% vs. 20%, respectively; log-rank p=0.03). The other RCT by Bui et al (18) has only been published in abstract form. In that study, no benefit in response rate was observed, and overall survival was not reported. One randomized phase II trial reported by Worden et al (22) examined the role of high-dose ifosfamide specifically. In that trial, no statistically significant improvements in overall or disease-free survival were observed between the high- and standard-dose chemotherapy arms. Although a number of small phase II trials have reported response rates of 31%-63% with overall median survival ranging from 13 months to 24 months, it is clear that this experience was not replicated in the RCTs.

Although none of the trials examined evaluated potentially myeloablative regimens similar to those utilized in other settings, such as hematological malignancies, it is quite clear that even modest dose escalations beyond standard-dose chemotherapy are associated with increased hematologic toxicity. Treatment-related deaths were also more common in the high-dose arms (seven deaths) than in the standard-dose arms (one death) in both phase III trials.

ONGOING TRIALS

The National Cancer Institute was searched during the development of this document, and no ongoing randomized trials of dose-intensive chemotherapy with growth factor or autologous bone marrow/stem cell transplant support in advanced or metastatic adult soft tissue sarcoma were identified. (Searched 2002 to May 2005)

CONCLUSIONS

Although one of the randomized trials reported that, at one year, progression-free survival was significantly longer in the high-dose chemotherapy arm, this systematic review has been unable to discern any consistent benefits in patients with metastatic unresectable soft tissue sarcoma when doses higher than standard-dose chemotherapy are employed in this setting. Future research in patients with inoperable locally advanced or metastatic soft tissue sarcoma should focus on the identification of novel compounds or combinations that improve the response rate or survival of those patients. If high-dose chemotherapy with growth factor support or autologous bone marrow/stem cell transplantation is to be pursued, potentially myeloablative combinations similar to those used in hematological malignancies should be compared to conventional approaches. Outcomes should include survival, response, response duration, symptom control, and quality of life.

CONFLICT OF INTEREST

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

JOURNAL REFERENCE

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REFERENCES

1. Potter DA, Glenn J, Kinsella T, Glatstein E, Lack EE, Restrepo C, et al. Patterns of recurrence in patients with high grade soft-tissue sarcomas. J Clin Oncol. 1985;3(3):353-66.
2. Frost DB. Pulmonary metastasectomy for soft tissue sarcomas: is it justified? J Surg Oncol. 1995;59:110-5.
3. Van Geel AN, Pastorino U, Jauch KW, Judson IR, van Coevorden F, Buesa J, 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.
4. 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;4:103-12.
5. Antman KH, Montella D, Rosenbaum C, Schwen M. Phase II trial of ifosfamide with mesna in previously treated metastatic sarcoma. Cancer Treat Rep. 1985;69:499-504.
6. Schutte J, Kellner R, Seeber S. Ifosfamide in the treatment of soft-tissue sarcomas: experience at the West German Tumor Center, Essen. Cancer Chemother Pharmacol. 1993;31(Suppl 2):S194-S198.
7. Bramwell VHC, Mouridsen HT, Santoro A, Blackledge G, Somers R, Verweij J, et al. Cyclophosphamide versus ifosfamide: a randomized phase II trial in adult soft-tissue sarcomas. Cancer Chemother Pharmacol. 1993;31(Suppl 2):S180-S184.
8. 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.
9. O'Bryan RM, Baker LH, Gottlieb JE, Rivkin SE, Balcerzak SP, Grumet GN, et al. Dose response evaluation of adriamycin in human neoplasia. Cancer. 1977;39:1940-8.
10. Elias A, Ryan L, Aisner J, Antman KH. Mesna, doxorubicin, ifosfamide, dacarbazine (MAID) regimen for adults with advanced sarcoma. Semin Oncol. 1990;17(2 Suppl 4):41-9.
11. Le Cesne A, Antoine E, Spielmann M, Le Chevalier T, Brain E, Toussaint C, et al. High-dose ifosfamide: circumvention of resistance to standard-dose ifosfamide in advanced soft tissue sarcomas. J Clin Oncol. 1995;13(7):1600-8.
12. Van Oosterom AT, Mouridsen HT, Nielsen OS, Dombernowsky P, Krzemieniecki K, Judson I, et al. Results of randomised studies of the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) with two different ifosfamide regimens in first- and second-line chemotherapy in advanced soft tissue sarcoma patients. Eur J Cancer. 2002;38:2397-406.
13. Steward WP, Verweij J, Somers R, Spooner D, Kerbrat P, Clavel M, et al. Granulocyte-macrophage colony-stimulating factor allows safe escalation of dose-intensity of chemotherapy in metastatic adult soft tissue sarcomas: a study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group.[comment]. J Clin Oncol. 1993;11(1):15-21.
14. Bui BN, Chevallier B, Chevreau C, Krakowski I, Peny AM, Thyss A, et al. Efficacy of lenograstim on hematologic tolerance to MAID chemotherapy in patients with advanced soft tissue sarcoma and consequences on treatment dose-intensity. J Clin Oncol. 1995;13(10):2629-36.

15. Michelotti A, Romanini A, Giannessi P, Bengala C, Conte P. Accelerated epirubicin-ifosfamide-dacarbazine regimen in patients with adult soft tissue sarcomas. Am J Clin Oncol. 1996;19(1):78-81.
16. 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.
17. Le Cesne A, Judson I, Crowther D, Rodenhuis S, Keizer HJ, Van Hoesel Q, et al. Randomized phase III study comparing conventional-dose doxorubicin plus ifosfamide versus high-dose doxorubicin plus ifosfamide plus recombinant human granulocyte-macrophage colony-stimulating factor in advanced soft tissue sarcomas: A trial of the European Organization for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group. J Clin Oncol. 2000;18(14):2676-84.
18. Bui NB, Demaille MC, Chevreau C, Blay JY, Cupissol D, Rios M, et al. qMAID vs MAID + 25% with G-CSF in adults with advanced soft tissue sarcoma (STS). First results of randomized study of the FNCLCC sarcoma group [abstract]. Proc Am Soc Clin Oncol. 1998;17:517a, Abstract 1991.
19. Patel SR, Vadhan-Raj S, Burgess MA, Papadopoulos NE, Plager C, Jenkins J, et al. Dose-intensive chemotherapy with adriamycin, ifosfamide and growth factors in chemotherapy naive patients with soft tissue sarcomas [abstract]. Sarcoma. 1997;1(3&4):198.
20. De Pas T, de Braud F, Orlando L, Nole F, Munzone E, Zampino MG, et al. High-dose ifosfamide plus adriamycin in the treatment of adult advanced soft tissue sarcomas: is it feasible?[comment]. Ann Oncol. 1998;9(8):917-9.
21. Maurel J, Fra J, Lopez-Pousa A, Garcia dM, X, Balana C, Casado A, et al. Sequential dose-dense doxorubicin and ifosfamide for advanced soft tissue sarcomas: a Phase II trial by the Spanish Group for Research on Sarcomas (GEIS). Cancer. 2004;100(7):1498-506.
22. Worden FP, Taylor JMG, Biermann JS, Sondak VK, Leu KM, Chugh R, et al. Randomized phase II evaluation of 6 g/m^2 of ifosfamide plus doxorubicin and granulocyte colony-stimulating factor (G-CSF) compared with 12 g/m^2 of ifosfamide plus doxorubicin and G-CSF in the treatment of poor-prognosis soft tissue sarcoma. J Clin Oncol. 2005;23(1):105-12.
23. Lin T-Y, Guang Z-Z, Su Y-S, Zhou Z-M, Liu D-G. High dose ifosfamide, doxorubicin, dacarbazine and G-CSF for patients with metastatic or locally advanced soft tissue sarcoma. Chin J Cancer Res. 1999;11(3):200-3.
24. Schlemmer M, Wendtner CM, Falk M, Lindner LH, Abdel-Rahman S, Salat C, et al. Efficacy of consolidation high-dose chemotherapy (HDCT) with ifosfamide, carboplatin and etoposide followed by peripheral blood stem cell rescue (PBSCR) in chemosensitive patients with metastatic soft tissue sarcomas [abstract]. J Clin Oncol (Meeting Abstracts). 2004;22(14 Suppl):Abstract 9014.
25. Deckert PM, Siehl JM, Thiel E, Schmittel A, Hutter G, Szelenyi H, et al. Phase II study of liposomal daunorubicin and ifosfamide (IDx) as first line chemotherapy in soft tissue sarcoma [abstract]. J Clin Oncol (Meeting Abstracts). 2004;22(14 Suppl):Abstract 9011.
26. Reichardt P, Tilgner J, Hohenberger P, Dorken B. Dose-intensive chemotherapy with ifosfamide, epirubicin, and filgrastim for adult patients with metastatic or locally advanced soft tissue sarcoma: a phase II study. J Clin Oncol. 1998;16(4):1438-43.
27. Palumbo R, Neumaier C, Cosso M, Bertero G, Raffo P, Spadini N, et al. Dose-intensive first-line chemotherapy with epirubicin and continuous infusion ifosfamide in

adult patients with advanced soft tissue sarcomas: a phase II study. Eur J Cancer. 1999;35(1):66-72.
28. Saeter G, Alvegard TA, Monge OR, Strander H, Turesson I, Klepp R, et al. Ifosfamide and continuous infusion etoposide in advanced adult soft tissue sarcoma. A Scandinavian Sarcoma Group Phase II Study. Eur J Cancer. 1997;33(10):1551-8.
29. Buesa JM, Lopez-Pousa A, Martin J, Anton A, Garcia del Muro J, Bellmunt J, et al. Phase II trial of first-line high-dose ifosfamide in advanced soft tissue sarcomas of the adult: a study of the Spanish Group for Research on Sarcomas (GEIS). Ann Oncol. 1998;9(8):871-6.
30. Frustaci S, Buonadonna A, Galligioni E, Favaro D, De Paoli A, Lo Re G, et al. Increasing 4'-epidoxorubicin and fixed ifosfamide doses plus granulocyte-macrophage colony-stimulating factor in advanced soft tissue sarcomas: a pilot study. J Clin Oncol. 1997;15(4):1418-26.
31. Frustaci S, Buonadonna A, Romanini A, Comandone A, Dalla Palma M, Gamucci T, et al. Increasing dose of continuous infusion ifosfamide and fixed dose of bolus epirubicin in soft tissue sarcomas. A study of the Italian group on rare tumors. Tumori. 1999;85(4):229-33.
32. De Pas T, Curigliano G, Masci G, Catania C, Comandone A, Boni C, et al. Phase I study of twelve-day prolonged infusion of high-dose ifosfamide and doxorubicin as first-line chemotherapy in adult patients with advanced soft tissue sarcomas. Ann Oncol. 2002;13(1):161-6.
33. Bokemeyer C, Franzke A, Hartmann JT, Schober C, Arseniev L, Metzner B, et al. A phase I/II study of sequential, dose-escalated, high dose ifosfamide plus doxorubicin with peripheral blood stem cell support for the treatment of patients with advanced soft tissue sarcomas. Cancer. 1997;80(7):1221-7.
34. Chevreau C, Bui BN, Chevallier B, Krakowski I, Maugard C, Mihura J, et al. Phase I-II trial of intensification of the MAID regimen with support of lenograstim (rHuG-CSF) in patients with advanced soft-tissue sarcoma (STS). Am J Clin Oncol. 1999;22(3):267-72.
35. Chow W, Somlo G, Doroshow JH, Reardon D, ter Veer A, Leong L, et al. Sequential high-dose chemotherapy (HDCT) and peripheral blood progenitor cell rescue (PBPC) in young adults with soft tissue and bone sarcomas (SARC) [abstract]. Proc Am Soc Clin Oncol. 1998;17:512a, Abstract 1972.
36. Myong H, Rosen G, Forscher C, Hurvitz C, Hamburg S, Qasabian L, et al. High dose chemotherapy (CTX) with autologous peripheral stem cell transplantation (PSCT) for advanced sarcoma [abstract]. Proc Am Soc Clin Oncol. 1998;17:511a, Abstract 1971.
37. Kasper B, Meissner J, Harter C, Lehnert T, Bernd L, Egerer G. High-dose chemotherapy (HDCT) with autologous peripheral blood stem cell transplantation (PBSCT) for bone and soft tissue sarcomas [abstract]. Proc Am Soc Clin Oncol. 2003;22:817, Abstract 3283.
38. Blay JY, Bouhour D, Ray-Coquard I, Dumontet C, Philip T, Biron P. High-dose chemotherapy with autologous hematopoietic stem-cell transplantation for advanced soft tissue sarcoma in adults. J Clin Oncol. 2000;18(21):3643-50.
39. Falk MH, Salat C, Ochmann O, Knabe H, Mempel W, Sauer HJ, et al. High-dose chemotherapy (HDCT) with peripheral blood stem cell rescue (PBSCR) for adults with soft tissue sarcomas (STS) [abstract]. Proc Am Soc Clin Oncol. 1999;18:544a, Abstract 2102.

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Dose-intensive Chemotherapy with Growth Factor or Autologous Bone Marrow/Stem Cell Transplant Support in the First-line Treatment of Advanced or Metastatic Adult Soft Tissue Sarcoma: Guideline Development and External Review: Methods and Results

S Verma, J Younus, D Stys-Norman, AE Haynes, M Blackstein, and the Sarcoma Disease Site Group

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

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Each Evidence-Based Series is comprised of 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 dose-intensive chemotherapy for patients with inoperable locally advanced or metastatic STS, developed through systematic review, evidence synthesis, and input from practitioners in Ontario. This evidence-based series has been reviewed and approved by the Sarcoma DSG, which comprises medical oncologists, radiation oncologists, surgeons, a pathologist, a methodologist and community representatives. To find out more information regarding the Sarcoma DSG, please go to the CCO Web site at http://www.cancercare.on.ca/.

Report Approval Panel

Prior to the 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 a recommendation around the use of stem cell transplantation cannot be made given that insufficient data exists and that the recommendation did not specify the first-line treatment setting and questioned the inclusion of phase I and phase II trials assessing growth factors, given the availability of the RCTs.

To address the key RAP comments, the DSG created two separate recommendations, with one stating that a recommendation to support the use of bone marrow or stem cell transplantation could not be made due to insufficient data. The inclusion of 'first-line' was incorporated into the recommendations. The inclusion of the phase I and phase II trials was in part a reflection of the past practice of including those trial types and in part due to the DSGs desire to provide a detailed description of the efficacy and toxicity of the treatments.

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.

BOX 1: DRAFT RECOMMENDATIONS (approved for external review February 22, 2006)
Target Population Adult patients with inoperable locally advanced or metastatic soft tissue sarcoma.
Recommendation • High-dose chemotherapy with growth factor or autologous bone marrow/stem cell transplantation is not recommended for the routine treatment of patients with inoperable locally advanced or metastatic soft tissue sarcoma.
Qualifying Statements • High-dose chemotherapy with growth factor or autologous bone marrow/stem cell transplantation and standard-dose chemotherapy have similar adverse effects. These two treatment regimens have similar overall adverse events but high grade problems appear to be more prominent with high dose. However, grade 3/4 thrombocytopenia is significantly higher with high-dose regimens. Neutropenic fever and febrile neutropenia occur more frequently in high-dose regimens and the rate of treatment related deaths is also higher with high-dose regimens.

Methods

Feedback was obtained through a mailed survey of 74 practitioners in Ontario, which 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-three responses were received out of the 74 surveys sent (31% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, eight indicated that the report was relevant to their clinical practice, and they completed the survey. One practitioner indicated that the topic was relevant to them but did not complete the questionnaire as they do not work directly with patients. Therefore, their 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.	7 (100)	0	0
There is a need for a guideline on this topic.	6 (85.3)	1 (14.3)	0
The literature search is relevant and complete.	7 (100)	0	0
The results of the trials described in the report are interpreted according to my understanding of the data.	7 (100)	0	0
The draft recommendations in the report are clear.	7 (100)	0	0
I agree with the draft recommendations as stated.	7 (100)	0	0
This report should be approved as a practice guideline.	6 (85.3)	0	1 (14.3)

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 (85.3)	1 (14.3)	0

Summary of Written Comments

Of the eight respondents, one clinician provided suggestions for future document development and content. This was noted at the PEBC office. No other feedback was provided for this document

Modifications/Actions

No further modifications/actions in response to external review were required for this 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.

Contact Information

For further information about this series, please contact **Dr. Shailendra Verma**, Chair, Sarcoma Disease Site Group; Ottawa Regional Cancer Centre, General Division, 503 Smyth Road, Ottawa, Ontario K1H 1C4; TEL 613-737-7700 ext. 56792; FAX 613-247-3511.

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 E-mail: ccopgi@mcmaster.ca

REFERENCES

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;13:502-12.
2. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. J Clin Oncol. 1998;16(3):1226-31.

EBS 11-5 Document Assessment and Review Tool.

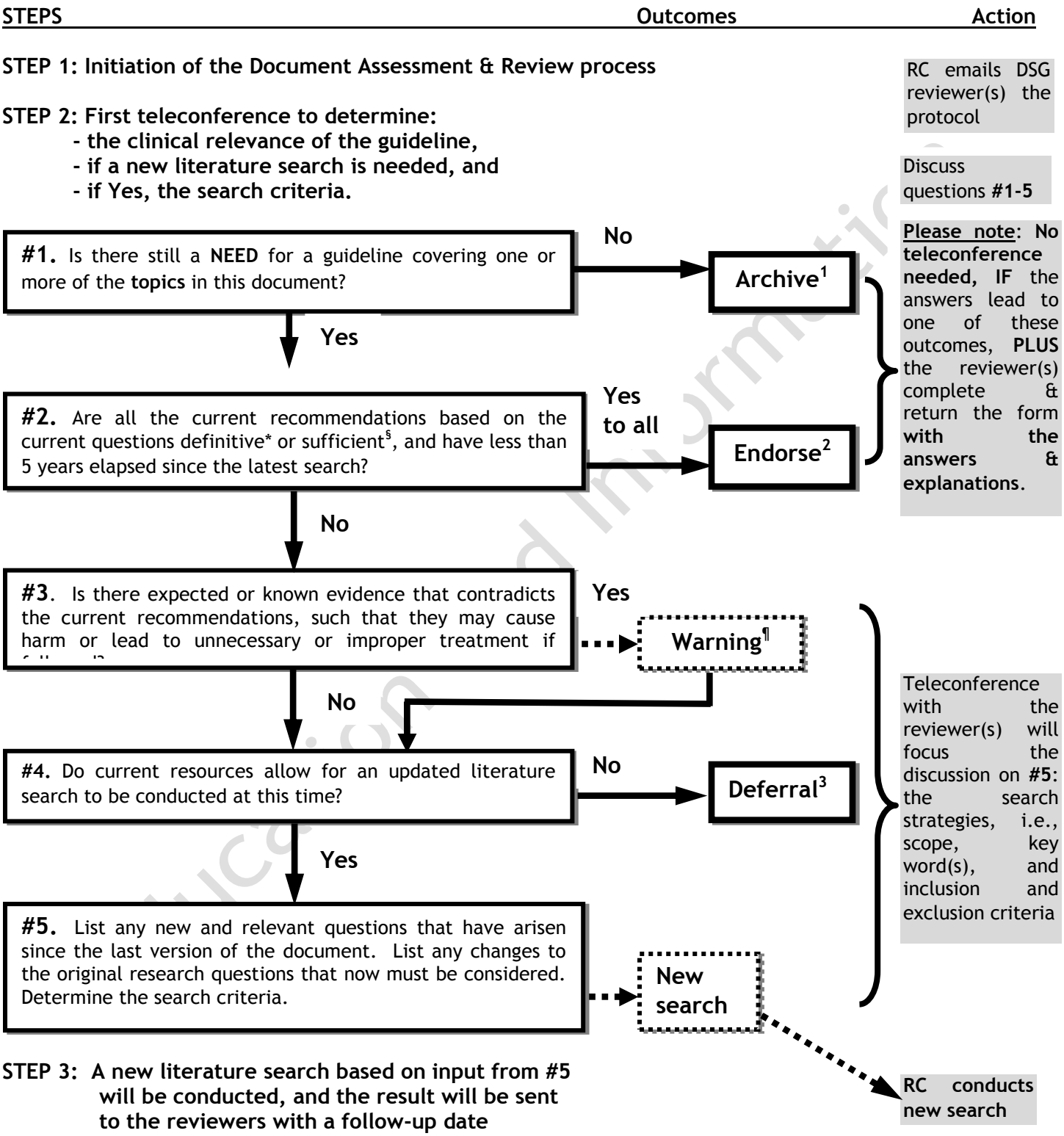
cancer care ontario | action cancer ontario
program in evidence-based care | programme de soins fondé sur des preuves

DOCUMENT ASSESSMENT AND REVIEW TOOL

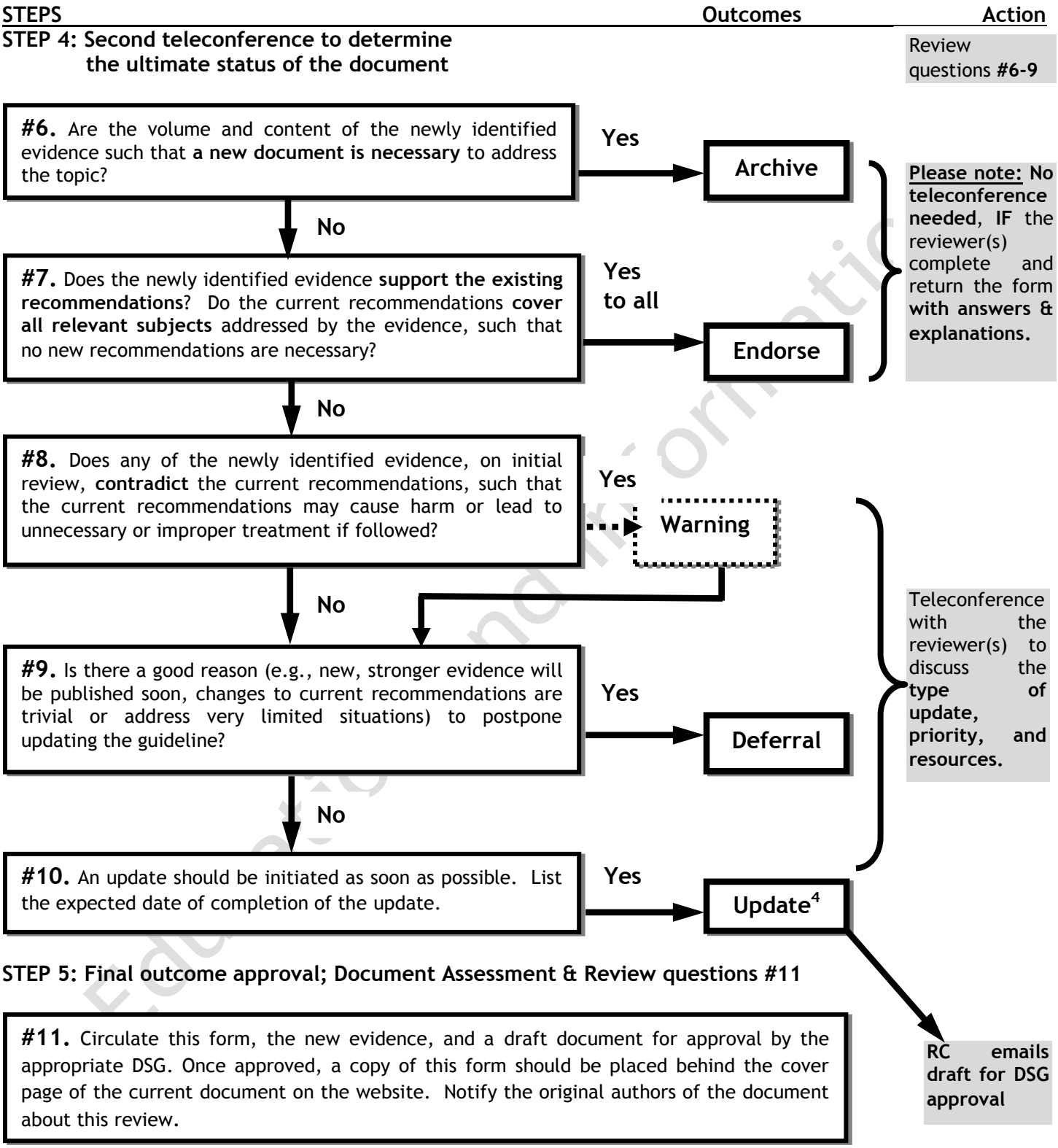
Number and title of document under review	**11-5: Dose-intensive Chemotherapy with Growth Factor or Autologous Bone Marrow/Stem Cell Transplant Support in Advanced or Metastatic Adult Soft Tissue Sarcoma**
Date of current version	11 April 2006
Clinical reviewer	Dr. Shailendra Verma
Research coordinator	Chika Agbassi
Date initiated	25 March 2011
Date and final results / outcomes	**11 April 2011- ARCHIVED**[1]
Instructions. Beginning at question 1, below, answer the questions in sequential order, following the instructions in the black boxes as you go.	
1. Is there still a need for a guideline covering one or more of the topics in this document **as is**? Answer Yes or No, and explain if necessary:	1.NO If No, then the document should be **ARCHIVED**[1] with no further action; **go to 11**. If Yes, then **go to 2**.
2. Are all the current recommendations based on the current questions **definitive**[*] or **sufficient**[§], and have less than **5 years elapsed** since the latest search? Answer Yes or No, and explain if necessary:	2. Not Applicable, document to be Archived If Yes, the document can be **ENDORSED**[2] with no further action; **go to 11**. If No, **go to 3**.
3. Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, providing references of known evidence:	3. Not Applicable. If Yes, the document should be taken off the website as soon as possible. A **WARNING**[¶] should be put in its place informing a user that the document is only available by email, with a brief explanation of the reasons. If No, g**o to 4**.
4. Do current resources allow for an updated literature search to be conducted at this time? Answer Yes or No, and explain as necessary. Provide an expected date of completion of the updated search, if applicable:	4. YES • there is a designated research co-ordinator at the PEBC to carry out the literature search If No, a **DEFERRAL**[3] should be placed on the document indicating it cannot be updated at this time, but will be reviewed again on a yearly basis. If Yes, go **to 5**.
5a. **Guideline Research Questions.** Please review the original guideline research questions below and if applicable, list any MINOR changes to the questions that now must be considered. If a question is no longer relevant, it can be deleted. The Document Assessment & Review process evaluates the guideline **as is** and CANNOT accommodate significant changes to the questions or the addition of new questions introducing new patient populations or new agents/interventions because if this what is required in order to make this guideline relevant, then a brand new document should be produced and this guideline as is should be	

ARCHIVED (i.e., go back to Q1 of this form and answer NO).	
• **No changes to the original questions**	
5b. **Inclusion and Exclusion criteria.** List below any changes to the selection criteria in the original version made necessary by new questions, changes to existing questions, or changes in available evidence (e.g., limit a search to randomized trials that originally included non-randomized evidence).	
• **No changes to the original inclusion and exclusion criteria**	
5c. Conduct an updated literature search based on that done for the current version and modified by 5a and 5b above. Report the results below.	
• **Not Applicable, document to be Archived**	
Go to 6.	
6. Is the volume and content of the new evidence so extensive such that a simple update will be difficult?	6. Not Applicable. If Yes, then the document should be **ARCHIVED** with no further action; **go to 11**. If No, **go to 7**.
7. On initial review, does the newly identified evidence support the **existing recommendations**? Do the current recommendations **cover all relevant subjects** addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No, and explain if necessary:	7. Not Applicable. If Yes, the document can be **ENDORSED**. If No, **go to 8**.
8. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:	8. Not Applicable. If Yes, a **WARNING** note will be placed on the web site. If No, **go to 9**.
9. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	9. Not Applicable. If Yes, the document update will be **DEFERRED**, indicating that the document can be used for decision making and the update will be deferred until the expected evidence becomes available. If No, **go to 10.**
10. An update should be initiated as soon as possible. List the expected date of completion of the update:	10. Not Applicable. An **UPDATE**[4] will be posted on the website, indicating an update is in progress.
11. Circulate this form to the appropriate Disease Site Group for their approval. Once approved, a copy of this form should be placed behind the cover page of the current document on the website. Notify the original authors of the document about this review.	
DSG Approval Date:	**May 31, 2011**
Comments from DSG members:	The issue of dose intense chemotherapy with the chemotherapy agents in question is no longer relevant

DOCUMENT ASSESSMENT & REVIEW 5-STEP FLOW CHART



FLOW CHART (cont.)



DOCUMENT ASSESSMENT AND REVIEW DEFINITIONS

Document Assessment and Review Terms

***Definitive recommendations** – Definitive means that the current recommendations address the relevant subject area so fully that it would be very surprising to identify any contradictory or clarifying evidence.

[§] **SUFFICIENT RECOMMENDATIONS** – Sufficient means that the current recommendations are based on consensus, opinion and/or limited evidence, and the likelihood of finding any further evidence of any variety is very small (e.g., in rare or poorly studied disease).

[¶]**WARNING** – A warning indicates that, although the topic is still relevant, there may be, or is, new evidence that may contradict the guideline recommendations or otherwise make the document suspect as a guide to clinical decision making. The document is removed from the website, and a warning is put in its place. A new literature search may be needed, depending on the clinical priority and resources.

Document Assessment and Review Outcomes

1. **ARCHIVED** – An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our Web site, **each page is watermarked** with the phrase "ARCHIVED".

2. **ENDORSED** – An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DEFERRAL** - A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action due to a number of reasons. The reasons for deferral should be found in the Document & Assessment Review form and on the document.

4. **UPDATE** – An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.