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## **Liposomal Anthracyclines in the Management of Patients with HIV-positive Kaposi's Sarcoma Practice Guideline Report #12-8**

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**ORIGINAL GUIDELINE: September 30, 2002**

**NEW EVIDENCE ADDED TO THE GUIDELINE REPORT: No new evidence**

**MOST RECENT LITERATURE SEARCH: June 2004**

There is currently no new evidence to inform the practice guideline report.

### **SUMMARY**

#### **Guideline Question**

Does liposomal anthracycline therapy have advantages over standard combination therapy for patients with human immunodeficiency virus (HIV)-positive Kaposi's sarcoma who have aggressive cutaneous or visceral disease? Outcomes of interest are survival, time-to-treatment failure, response rates, adverse effects, and quality of life.

#### **Target Population**

These recommendations apply to patients with HIV-positive Kaposi's sarcoma and good performance status (Eastern Cooperative Oncology Group [ECOG] 0-2) who have progressive cutaneous disease despite prior treatment with interferon and/or vinblastine, or who have visceral disease that is symptomatic or progressive.

#### **Recommendations**

- The use of conventional combination chemotherapy or single-agent liposomal anthracycline therapy, represent reasonable treatment options in the management of patients with HIV-positive Kaposi's sarcoma.

#### **Qualifying Statements**

- Many anti-viral regimens used in the treatment of HIV cause peripheral nerve damage. In patients with HIV-positive Kaposi's sarcoma, the risk of neuropathic toxicity appears to be greater with vinca alkaloid-containing conventional treatment regimens than with single-agent liposomal anthracyclines. Therefore, if patients have neuropathy, or are at significant risk for neurotoxicity, liposomal anthracycline therapy may be preferable to conventional combination chemotherapy.

## **Methods**

The literature was searched using the MEDLINE (Ovid) (1966 through August 2002), CANCERLIT (Ovid) (1983 through July 2002), and Cochrane Library (Issue 3, 2002) databases. In addition, the Physician Data Query clinical trials database, and abstracts published in the conference proceedings from the meetings of the American Society of Clinical Oncology (1995-2002), and the European Society for Medical Oncology (1998, 2000) were searched for reports of new or ongoing trials. The Canadian Medical Association Infobase and the National Guideline Clearinghouse databases were searched for relevant clinical practice guidelines. Reference lists from relevant articles and reviews were searched for additional trials.

Evidence was selected and reviewed by one member of the Practice Guidelines Initiative's Systemic Treatment Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Systemic Treatment Disease Site Group, which is comprised of medical oncologists, pharmacists, and one community representative.

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

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

## **Update**

The original literature search has been updated using MEDLINE (September 2002 through June 2004), EMBASE (September 2002 through June 2004), the Cochrane Library (Issue 2, 2004), the Physician Data Query database, the Canadian Medical Association Infobase, and the National Guideline Clearinghouse, as well as abstracts published in the proceedings of the meetings of the American Society of Clinical Oncology (2004), and the European Society for Medical Oncology (2002). Article bibliographies and personal files were also searched to June 2004 for evidence relevant to this practice guideline report. Please note that CANCERLIT is no longer included in update searches: results from an internal Practice Guidelines Initiative project indicated that the overlap with MEDLINE is 100%, making CANCERLIT database searches redundant.

## **Key Evidence**

- In three published randomized controlled trials, liposomal anthracycline formulations have produced response rates between 25% and 59%, with response rates for the control arm combination chemotherapy regimens ranging from 23% to 28%. In two of these trials, the response rates produced with the liposomal anthracycline formulations were significantly superior to the control chemotherapy regimens. To date, no statistically significant differences in survival or time-to-treatment failure have been seen.

## **Future Research**

- Patients with HIV-positive Kaposi's sarcoma should be encouraged to enter clinical trials designed to test therapies aimed at improving survival and quality of life, trials designed to assess whether there are clinically important differences between the available liposomal anthracycline formulations and trials comparing single-agent liposomal anthracyclines with single-agent non-liposomal anthracyclines.
- More information is required to provide better estimates of the risk of cardiotoxicity from liposomal anthracyclines.

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## **PREAMBLE: About Our Practice Guideline Reports**

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

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

### Reference:

<sup>1</sup> 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.

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## FULL REPORT

### I. QUESTION

Does liposomal anthracycline therapy have advantages over standard therapy for patients with HIV-positive Kaposi's sarcoma who have aggressive cutaneous or visceral disease? Outcomes of interest are survival, time-to-treatment failure, response rates, adverse effects, and quality of life.

### II. CHOICE OF TOPIC AND RATIONALE

Kaposi's sarcoma (KS) is one of many malignancies that can occur with HIV infection. It is a heterogeneous disease, with a wide spectrum of disease manifestations ranging from lesions on isolated areas of the skin (cutaneous KS) to the involvement of internal organs, notably the lungs or gastrointestinal system (visceral KS). Cutaneous KS is an important cause of morbidity with significant impairment of activities of daily living leading to dependency, while visceral KS can be life-threatening (please see Appendix 1 for staging information) (1).

Treatment decisions for patients with KS must take into consideration the extent and rate of tumour growth, symptoms, immune system condition, and concurrent complications of HIV (2). The delivery of effective treatment for KS and the maintenance of adequate control of HIV and other infections are the current goals in the treatment of this malignancy (2). Treatment with interferon or vinblastine and anti-retroviral agents can be considered for many patients with non-aggressive cutaneous KS (2). The use of combined anti-retroviral therapy has led to a decline in the incidence of KS (3). However, the possibility exists that more KS will develop in these patients if the efficacy of the anti-retroviral therapy fades over time. Radiotherapy is often used in patients with localised cutaneous disease. However, radiotherapy is unlikely to be considered as the preferred form of therapy for the patients with aggressive cutaneous or visceral disease, which is the patient population considered for this guideline.

More aggressive chemotherapy programs, such as various combination chemotherapy regimens, are generally reserved for patients with cutaneous KS resistant to interferon or vinblastine, or for patients with more life-threatening sites of disease. Anthracycline-based chemotherapy, either in single-agent form, or in combination with other drugs such as bleomycin and vincristine, has been used to treat patients with visceral or aggressive cutaneous KS. Anecdotal information suggests that combination chemotherapy with doxorubicin, bleomycin, and vincristine is the initial treatment of choice for patients with aggressive cutaneous or visceral HIV-positive KS. This is the regimen that has been used in the control arm in some of the randomized trials of liposomal anthracyclines reviewed in this report (4,5).

While anthracycline-based chemotherapy produces responses in patients with HIV-positive aggressive cutaneous or visceral KS, it may do so with some degree of toxicity for patients. Moreover, even if these regimens are well-tolerated and produce the desired responses, there are concerns that protracted exposure to the drugs in these regimens will place the patient at risk for long-term refractory organ toxicity. Patients in whom tolerance of anthracyclines is exceeded may experience cardiomyopathy. Treatment with bleomycin may result in lung dysfunction or Raynaud's phenomenon in some patients. Vincristine use is associated with peripheral neuropathy, something these patients may be predisposed to because of the HIV or anti-retroviral agents used to control their infections. The development of a drug regimen less toxic but equally or more efficacious than current regimens would represent an improvement in the care of these patients.

Liposomal anthracycline agents were developed to deliver drugs to patients in a more selective manner. This action is related to the pharmacodynamics of these agents: they distribute themselves differently in body compartments and tissue compared to the unencapsulated (non-liposomal or free) agent. Theoretically, liposomal anthracyclines offer a therapeutic advantage over the free drug due to their prolonged circulation time and decreased

drug-induced toxicity (1,2). The favourable distribution profiles for these agents should theoretically enhance their therapeutic ratios. Liposomal anthracyclines (both doxorubicin and daunorubicin) have been developed and tested in patients with HIV-positive KS in phase III trials. The costs associated with these agents and their high profile in the HIV community motivated the Systemic Treatment Disease Site Group (STDSG) to examine currently available data to determine their potential role in the management of patients with HIV-positive Kaposi's sarcoma and to develop evidence-based recommendations for their use. The results of these studies are the subject of this report.

### **III. METHODS**

#### **Guideline Development**

This practice guideline report was developed by the Practice Guidelines Initiative (PGI), using the methodology of the Practice Guidelines Development Cycle (6). Evidence was selected and reviewed by one member of the PGI's STDSG and methodologists. Members of the STDSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on chemotherapy with liposomal anthracyclines in patients with HIV-positive Kaposi's sarcoma, developed through systematic reviews, evidence synthesis and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ministry of Health and Long-Term Care.

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

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

#### **Literature Search Strategy**

The literature was searched using the MEDLINE (Ovid) (1966 through August 2002), CANCELIT (Ovid) (1983 through July 2002), and Cochrane Library (Issue 3, 2002) databases. In addition, the Physician Data Query clinical trials database, and abstracts published in the conference proceedings from the meetings of the American Society of Clinical Oncology (1995-2002), and the European Society for Medical Oncology (1998, 2000) were searched for reports of new or ongoing trials. The Canadian Medical Association Infobase and the National Guideline Clearinghouse databases were searched for relevant clinical practice guidelines. Relevant articles and abstracts were selected and reviewed by one member of the STDSG and methodologists, and the reference lists from these sources were searched for additional trials.

The literature search combined the disease specific terms (sarcoma, kaposi/ or kaposi:.tw. and HIV/ or HIV.mp. or HIV infections/ or human immunodeficiency virus.tw. or AIDS/) with treatment specific terms (drug therapy/ or anthracyclines/ or anthracyclines.mp. or liposome:.and doxorubicin.mp. or liposome:.and daunorubicin.mp or doxil.tw. or caelyx.tw. or liposom:.mp. or daunoxome.tw.) with search specific terms for the following study designs: practice guidelines, systematic reviews or meta-analyses, reviews, randomized controlled trials, and clinical trials.

## **Update**

The original literature search has been updated using MEDLINE (September 2002 through June 2004), EMBASE (September 2002 through June 2004), the Cochrane Library (Issue 2, 2004), the Physician Data Query database, the Canadian Medical Association Infobase, and the National Guideline Clearinghouse, as well as abstracts published in the proceedings of the meetings of the American Society of Clinical Oncology (2004), and the European Society for Medical Oncology (2002). Article bibliographies and personal files were also searched to June 2004 for evidence relevant to this practice guideline report. Please note that CANCERLIT is no longer included in update searches: results from an internal PGI project indicated that the overlap with MEDLINE is 100%, making CANCERLIT database searches redundant.

## **Inclusion Criteria**

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

1. Randomized controlled trials (RCTs) comparing a liposomal anthracycline regimen to observation, placebo or another chemotherapy regimen for the treatment of HIV-positive Kaposi's sarcoma.
2. Reported data on outcomes of interest including survival, time-to-treatment-failure, response rates, adverse effects, and quality of life.
3. Trials reporting on patients with aggressive cutaneous or visceral HIV-positive KS.

## **Exclusion Criteria**

1. Phase I and II studies were not considered, because of the availability of randomized controlled trials.
2. Letters, editorials, and review articles were not included in this report.
3. Papers published in a language other than English were not considered.
4. Trials including only patients with non-aggressive cutaneous KS were not considered.

## **Synthesizing the Evidence**

The treatment and control arms were different in each of the eligible reviewed trials. The experimental arms of the reviewed trials varied, with three trials using liposomal doxorubicin, and the fourth examining liposomal daunorubicin. The control arms also varied, with the chemotherapy regimens consisting of a combination of doxorubicin, bleomycin, and vincristine in two trials, bleomycin and vincristine in one trial and liposomal doxorubicin, bleomycin, and vincristine in one trial. Therefore, it was judged inappropriate by the STDSG to pool the data by performing a meta-analysis.

## **IV. RESULTS**

### **Literature Search Results**

A total of five randomized controlled trials (RCTs) were identified (4,5,7-9) in which patients in one of the treatment arms received a liposomal anthracycline.

The randomized trial, by Uthayakumar et al (7), employed a crossover design in which patients with HIV-positive Kaposi's sarcoma received no therapy and then went on to receive liposomal daunorubicin at the time of disease progression in the observation arm, or 12 weeks later. The patient group was restricted to individuals with non-aggressive cutaneous disease only and therefore did not meet the inclusion criteria as stated. Consequently, this study will not be discussed further.

The randomized trial reported by Mitsuyasu et al (8) is available only in abstract form at this time. In this study, patients with advanced-stage HIV-positive KS who had not received prior chemotherapy were randomized to receive either liposomal doxorubicin alone or combined with

bleomycin and vincristine. This study is described separately in the Outcomes section, as the treatment regimen is not directly comparable to that of the other eligible trials.

The remaining three studies were randomized controlled trials with sample sizes ranging from 232 to 258 patients (4,5,9). In the study reported by Stewart et al (9), the control arm consisted of a non-anthracycline combination regimen, while a combination anthracycline regimen was used as the control treatment in the studies of Gill (4) and Northfelt (5). Two of the RCTs used liposomal doxorubicin as the liposomal anthracycline (5,9), while the third RCT used liposomal daunorubicin (4). Gill et al (4) excluded patients who had received any prior systemic chemotherapy. Northfelt et al (5) excluded patients if they had received any prior anthracycline chemotherapy, or other chemotherapy within four weeks of entry into the study. Stewart et al (9) excluded patients who had received previous cytotoxic chemotherapy or interferon treatment in the preceding four weeks before entering into the study, or more than one cycle of bleomycin or vincristine at any time. These three studies are described in Table 1, and results are presented in Table 2.

**Table 1. Description of randomized controlled trials of liposomal anthracyclines.**

Study (ref.)	Patient Population	# rand. (# eval.)	Liposomal Anthracycline Regimen	Control Group Description	Outcome Variables
Gill et al, 1996 (4)	advanced KS*	232 (227)	liposomal daunorubicin 40 mg/m <sup>2</sup> IV every 2 weeks	doxorubicin 10 mg/m <sup>2</sup> , bleomycin 15 U, vincristine 1 mg IV every 2 weeks	response rate, survival, adverse effects, quality of life, time-to-treatment-failure
Northfelt et al, 1998 (5)	progressive KS†	258 (258)	liposomal doxorubicin 20 mg/m <sup>2</sup> IV every 2 weeks	doxorubicin 20 mg/m <sup>2</sup> , bleomycin 10 mg/m <sup>2</sup> , vincristine 1 mg IV every 2 weeks	response rate, adverse effects, survival, time-to-treatment-failure
Stewart et al, 1998 (9)	progressive KS‡	241 (218)	liposomal doxorubicin 20 mg/m <sup>2</sup> IV every 3 weeks	vincristine 1.4 mg/m <sup>2</sup> , bleomycin 15 mg/m <sup>2</sup> IV every 3 weeks	response rate, adverse effects, survival, time-to-treatment-failure

NOTE: # eval. = number of evaluable patients; # rand. = number of patients randomized; IV = intravenously; KS = Kaposi's sarcoma.

\* defined as the presence of  $\geq 25$  mucocutaneous lesions, symptomatic visceral involvement, or the presence of tumour-associated lymphedema.

† defined as progressive HIV-positive KS with at least 25 mucocutaneous lesions, the development of 10 or more new lesions in the preceding month or documented visceral disease.

‡ defined as progressive HIV-positive KS with at least 15 mucocutaneous lesions, the development of more than five cutaneous lesions in the preceding month or documented visceral KS with at least five assessable cutaneous lesions.

## Outcomes

In examining the results for the population of randomized patients, there were no significant differences in median survival time or time-to-treatment-failure between the treatment arms for any of the studies in which these endpoints were measured (Table 2).

In terms of response, Gill et al (4) detected no significant difference in response rates when liposomal daunorubicin was compared with a combination regimen that contained a different anthracycline given at a lower dose intensity (4). In the study reported by Northfelt et al (5), the objective response rate for patients receiving liposomal doxorubicin was 46% versus 25% for those patients receiving a combination of doxorubicin, bleomycin, and vincristine (ABV) ( $p < 0.001$ ). Stewart et al (9) observed an objective response rate of 59% in patients receiving liposomal doxorubicin versus 23% in patients receiving bleomycin and vincristine (BV) ( $p < 0.001$ ). However, patients in the control arm of this study did not receive an anthracycline as part of their chemotherapy regimen.

The percentage of patients with visceral disease in these studies ranged from 31% in the study by Gill et al (4) to 43% in the study by Stewart et al (9). The study by Northfelt et al (5) did not separate patients with visceral disease from those patients with aggressive cutaneous disease. In the study by Gill et al (4), 45% of the patients with visceral KS randomized to receive

liposomal daunorubicin had improvement in visceral disease, with 29% achieving a major response. In the group of patients receiving ABV, 55% of the patients with visceral KS had documented evidence of improvement, with 33% achieving a major response. In this study, survival was significantly improved for patients without visceral involvement at study entry ( $p=0.0045$ ), independent of treatment. When survival outcome by treatment arm was evaluated separately according to baseline visceral involvement, the difference in median survival was not significant (no data reported). Stewart et al (9) were able to obtain data from 104 patients who had symptoms attributed to visceral KS. Treatment with liposomal doxorubicin decreased the incidence of symptomatic pulmonary KS from 23.1% to 10.6% ( $p=0.002$ ) and symptomatic gastrointestinal KS from 16.3% to 3.8% ( $p<0.001$ ). Symptoms of gastrointestinal and pulmonary KS were not found to be significantly reduced in patients treated with BV. If the examination of activity is restricted to the subgroup of patients with visceral KS, it appears there was a pattern consistent with greater improvement in visceral symptoms seen more often with the liposomal agent in the Stewart study (9) that was not repeated in the Gill report (4).

In the Mitsuyasu et al (8) study reported in abstract form, 129 patients with aggressive cutaneous or visceral HIV-positive Kaposi's sarcoma were randomized to receive either liposomal doxorubicin at a dose of 20 mg/m<sup>2</sup> every two weeks or liposomal doxorubicin at the same dose combined with vincristine 1 mg and bleomycin 10 U/m<sup>2</sup> every two weeks. Since both treatment groups received a liposomal anthracycline, the results of this study were not directly comparable with the other reviewed randomized trials (4,5,9). Response rates were similar in both groups, with an objective response rate of 79% for the liposomal doxorubicin arm versus 80% for the combination arm. There were no significant differences between the two treatment groups for time-to-treatment failure or survival.

**Table 2. Results of randomized trials of liposomal anthracyclines.**

Reference	# entered (# eval.)	Treatment	Objective response rate (%)*		Time-to-treatment-failure (days)		Median Survival (days)	
Gill et al, 1996 (4)	117 (116)	lipo daun	25%	p=NS	115	p=0.13	369	p=0.19
	115 (111)	ABV	28%		99		342	
Northfelt et al, 1998 (5)	133 (133)	lipo dox	46%	p<0.001	124	p=0.26	160	p=NR
	125 (125)	ABV	25%		128		160	
Stewart et al, 1998 (9)	121 (116)	lipo dox	59%	p<0.001	160	p=NR	NR†	
	120 (102)	BV	23%		157			

NOTE: # = number; A = Adriamycin (doxorubicin); B = bleomycin; daun = daunorubicin; dox = doxorubicin; eval. = evaluable; lipo = liposomal; NS = not significant; NR = not reported; V = vincristine.

\* includes complete and partial responses

† this study reported mean survival times of 239 days for liposomal doxorubicin, versus 160 days for bleomycin and vincristine.

### Adverse Effects

In the study by Gill et al (4), patients treated with ABV experienced significantly more alopecia (36% versus [v.] 8%;  $p<0.0001$ ) and neuropathy (41% v. 13%;  $p<0.0001$ ) of any grade compared with patients treated with liposomal daunorubicin. With respect to hematologic toxicity, the incidence of grade 4 neutropenia was significantly higher in patients treated with liposomal daunorubicin versus patients treated with ABV (15% v. 5%;  $p=0.021$ ). Sixteen patients treated with liposomal daunorubicin and 31 patients treated with ABV discontinued treatment. Reasons for the discontinuation of treatment with liposomal daunorubicin included death due to complications of HIV infection, patient decision, loss to follow-up evaluation, opportunistic infection, and drug toxicity. The reasons for the discontinuation of ABV were similar, with the addition of intolerable nausea and vomiting, neuropathy, alopecia, and hand-foot syndrome. Thirty-six percent of patients receiving liposomal daunorubicin developed an opportunistic infection versus 26% of patients receiving ABV chemotherapy. This difference was not statistically significant. Seventeen percent of patients in the liposomal daunorubicin group

developed neutropenic fever, but no documented infection, compared with 11% of patients in the ABV group. Cardiac events (arrhythmia, palpitations, tachycardia, and hypertension) were observed in 6% of patients receiving liposomal daunorubicin and 9.9% of ABV patients.

In the study by Northfelt et al (5), thirty-seven percent of ABV patients and 11% of liposomal doxorubicin patients discontinued treatment because of an adverse event ( $p < 0.001$ ). One patient who received liposomal doxorubicin died as a result of cardiomyopathy. Eight patients (6%) who received liposomal doxorubicin and three patients (2%) who received ABV experienced episodes of sepsis. Opportunistic infections occurred in 37% of patients treated with liposomal doxorubicin and 30% of patients treated with ABV. The most common adverse event in both groups in the study was leucopenia, but the difference in frequency between the two study arms was not significant. However, there were significant differences between the two arms on other measures of toxicity greater than grade 3. Significantly more patients receiving ABV experienced nausea and/or vomiting (34% v. 15%;  $p < 0.001$ ), alopecia (19% v. 1%;  $p < 0.001$ ), and peripheral neuropathy (14% v. 6%;  $p = 0.002$ ). Mucositis was significantly more common in patients receiving liposomal doxorubicin (5% v. 2%;  $p = 0.026$ ), compared with patients receiving ABV. Three cases of hand-foot syndrome were observed in the liposomal doxorubicin arm versus one in the ABV arm.

Stewart et al (9) reported that the incidence of paresthesia (14% v. 3%;  $p < 0.005$ ), peripheral neuropathy ( $p < 0.001$ ), and constipation (11% v. 2%;  $p < 0.01$ ) were significantly higher in patients who received BV than in patients who received liposomal doxorubicin. The incidence of grade 3 leucopenia (72% v. 51%;  $p < 0.001$ ) and oral candidiasis (29% v. 18%;  $p < 0.05$ ) was significantly higher in patients receiving liposomal doxorubicin. Significantly more patients randomized to receive liposomal doxorubicin experienced an opportunistic infection, compared to patients who were randomized to receive BV (50% v. 30%;  $p < 0.002$ ). Other adverse effects were reported in similar frequencies in the two groups. In this study, patients who received BV were more likely to withdraw from the study prematurely due to a chemotherapy-related event (27%) versus those randomized to receive the liposomal anthracycline (11%).

Only one fully reported study (5) used equimolar doses of an anthracycline and the liposomal agent. In this study, a small and non-significant increase in leucopenia was noted for the liposomal arm. In the other studies where increased myelosuppression was noted, it may have been a reflection of the dose of the myelosuppressive agent used in the study.

The use of the other agents in combination with an anthracycline was associated with greater degrees of neuropathy and paresthesia, which appears to have been a contributing factor in discontinuing therapy in at least one study (5). It is important to report that one cardiotoxic death was recorded in a patient receiving liposomal doxorubicin in the Northfelt study (5). This event is consistent with the manufacturer's statement that the use of the liposomal formulation is not a guarantee against the possibility of anthracycline cardiotoxicity. The impact of the cardioprotectant dexrazoxane on the frequency of cardiotoxicity in patients treated with liposomal anthracycline formulations is unknown.

### **Quality of Life**

Quality of life (QOL) was assessed in the study by Gill et al (4) at each treatment cycle, using the Karnofsky performance status (KPS) score. In addition, a QOL patient questionnaire was completed every other cycle, consisting of questions that encompassed a general health survey, daily activities, treatment-specific symptoms and overall physical and emotional well-being. In this trial, baseline data on KPS and QOL scores were available from over 200 patients. At the end of 20 cycles of treatment, data on KPS scores were available on 11 patients and data on QOL scores were available on 6 patients. There were no statistically significant differences in KPS or QOL scores at any of the time points measured for patients treated with liposomal daunorubicin compared with patients treated with ABV, however, given that the authors of this

trial did not provide details on missing data, quality of life results from this trial must be interpreted with caution.

Quality of life was also assessed in the Northfelt study (5). The data related to quality of life were reported in a separate publication (10). Quality of life assessments were carried out using a validated 30-item, self-report, AIDS-modified questionnaire with eleven domains. Baseline data were available on 118 patients in the liposomal doxorubicin arm and 114 patients in the ABV arm, and data at end of treatment were available on over 70% of the treatment population. When the change from baseline to the end of treatment was compared between the two treatment arms, patients receiving liposomal doxorubicin showed significant improvements in four of the eleven domains (general health, pain, social functioning, and energy/fatigue) compared to patients receiving ABV. The domains with the greatest improvement in the liposomal doxorubicin arm compared to the ABV arm were general health and pain.

## **V. INTERPRETIVE SUMMARY**

As previously mentioned, liposomal anthracyclines were developed to be delivered to patients in a more selective manner than standard anthracyclines, theoretically offering a therapeutic advantage due to prolonged circulation time and decreased drug-induced toxicity. However, as none of the identified randomized trials included a control arm of single-agent anthracycline therapy, it is difficult to determine any incremental benefit of liposomal agents over conventional anthracyclines alone in terms of efficacy, toxicity or quality of life. While this is an important area for future research, the focus of this report remains on the currently available evidence of three randomized trials of single-agent liposomal anthracyclines compared with combination chemotherapy containing vincristine and bleomycin with or without doxorubicin.

In three published randomized controlled trials, liposomal anthracycline formulations produced response rates between 25% and 59%, compared with 23% to 28% for the control arm combination chemotherapy regimens. In two of these trials, the response rates were significantly superior with liposomal doxorubicin versus combination chemotherapy. Of these two trials, one trial included an anthracycline in the control arm while the other did not. No statistically significant differences in median survival or time-to-treatment-failure were detected in any of the three trials.

In terms of adverse events, rates of severe toxicity and opportunistic infection appear to be roughly equivalent between liposomal anthracycline therapy and conventional chemotherapy. However, it is clear that vincristine and bleomycin contribute significantly to toxicity, notably neurotoxicity. Therefore, if patients have neuropathy, or are at significant risk for neurotoxicity, the use of a liposomal anthracycline agent is a very attractive alternative to the commonly used combination regimen of doxorubicin, bleomycin, and vincristine. While not all patients with Kaposi's sarcoma develop neurotoxicity on conventional chemotherapy, many are on anti-retroviral regimens that may cause peripheral nerve damage, and many develop signs and symptoms of neurotoxicity as a result of these therapies.

Of the two randomized trials that report data on quality of life, one trial did not detect any significant differences in quality of life measures for patients in either treatment arm. Evidence from the other trial supports that aspects of quality of life are significantly better when patients are treated with liposomal anthracycline therapy compared to conventional combination therapy. However, it is unclear to what extent the changes described are clinically meaningful.

Based on this limited available information, the use of liposomal therapy or conventional combination therapy represents equally valid approaches in the treatment of patients with HIV-positive Kaposi's sarcoma. Patients should be informed of the harms and benefits associated with each treatment regimen and patient preference should be taken into account when making treatment decisions.

If a liposomal agent is to be used, there is insufficient information available to decide if one agent is superior to the other, or if liposomal anthracyclines are better than single-agent anthracycline therapy alone. These would be fruitful avenues for future research.

## **VI. ONGOING TRIALS**

The STDSG is aware of the following ongoing trials evaluating liposomal anthracyclines in patients with Kaposi's sarcoma:

**RPCI-DS-96-28, NCI-G97-1241, SEQUUS-30-38:** Phase III randomized study of liposomal doxorubicin in patients with AIDS-related Kaposi's sarcoma (11). Patients will be randomly assigned to receive liposomal doxorubicin or liposomal daunorubicin in a 3:1 ratio. Eighty patients will be studied to determine tumour response, safety and clinical benefit of liposomal doxorubicin. Preliminary results of this trial have been reported in abstract form (12). The Systemic Treatment DSG will monitor the literature for mature results from this trial.

**E-1D96:** Phase III randomized study of paclitaxel versus liposomal doxorubicin in patients with advanced AIDS-associated Kaposi's sarcoma (13). Two hundred and forty patients will be accrued and randomized to receive either paclitaxel or liposomal doxorubicin. Progression-free survival, quality of life, toxicity, and response rates will be measured. The summary was last modified on the PDQ web site in July 2002.

## **VII. DISEASE SITE GROUP CONSENSUS PROCESS**

A preliminary draft of this practice guideline report was circulated to the members of the STDSG for comment. The discussions at the DSG meetings highlighted the need to identify the patient group to whom this guideline was directed. The discussion also focused at some length on the interpretation of the data. Special care was taken to ensure that the information was conveyed in a manner that would be helpful to practitioners. As a result of these discussions, the initial draft of the practice-guideline-in-progress was modified. The modified version was recirculated to the STDSG for further comments before being sent for feedback from physicians involved in the care of patients with HIV-positive Kaposi's sarcoma.

## **VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT**

### **Draft Recommendations**

Based on the evidence above, the STDSG drafted the following recommendations:

#### ***Target Population***

These recommendations apply to patients with HIV-positive Kaposi's sarcoma and good performance status (ECOG 0-2) who have progressive cutaneous disease despite prior treatment with interferon and/or vinblastine, or who have visceral disease that is symptomatic or progressive.

#### ***Recommendations***

##### ***Key recommendations***

- The first choice of therapy for these patients should be conventional anthracycline regimens. However, in circumstances where the risk of toxicity from standard chemotherapy is likely to compromise a patient's health, a liposomal anthracycline represents an appropriate alternative treatment choice.

##### ***Qualifying statements***

- Many anti-viral regimens used in the treatment of HIV cause peripheral nerve damage, and the risk of neuropathic toxicity appears to be greater with vinca alkaloid-containing

conventional treatment regimens than with single-agent liposomal anthracyclines in patients with HIV-positive Kaposi's sarcoma. Therefore, liposomal anthracycline formulations represent a reasonable alternative to currently available chemotherapy regimens for patients with pre-existing neuropathy or those at high risk of neuropathy.

### ***Future Research***

- Patients with HIV-positive Kaposi's sarcoma should be encouraged to enter clinical trials designed to test therapies aimed at improving survival and quality of life, trials designed to assess whether there are clinically important differences between the available liposomal anthracycline formulations and trials comparing single-agent liposomal anthracyclines with single-agent non-liposomal anthracyclines.
- More information is required to provide better estimates of the risk of cardiotoxicity from liposomal anthracyclines.

### **Practitioner Feedback**

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

### ***Methods***

Practitioner feedback was obtained through a mailed survey of nine practitioners in Ontario (seven medical oncologists and two hematologists). The survey consisted of 21 items evaluating the methods, results, and interpretive summary used to inform the draft recommendations outlined and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey have been reviewed by the Systemic Treatment Disease Site Group.

### ***Results***

Key results of the practitioner feedback survey are summarized in Table 3. Six (67%) surveys were returned. Six (100%) respondents indicated that the practice-guideline-in-progress report was relevant to their clinical practice and completed the survey.

### ***Summary of Main Findings***

Two (33%) respondents provided written comments. The main points were:

1. One respondent asked whether the KS that might return after the current anti-retroviral therapies fail will be clinically the same as that treated in the studies reported, or whether the results of this guideline will be relevant to those events with the testing of new therapies.
2. A second respondent noted there was not strong support for the liposomal formulations in terms of survival and asked about quality of life benefits.

### ***Modifications/Actions***

1. While this may be true, there is merit in having a guideline for the current cohort of patients. No changes were made to the document.
2. The current guideline does not support the use of liposomal anthracyclines on the basis of survival enhancement, but does note the potential for benefit in a subset of patients at risk for complications from conventional combination chemotherapy, based on the reports of increased neurotoxicity for these treatments (9). No changes were made to the document.

**Table 3. Practitioner 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 clinical practice guideline, as stated in the “ <i>Choice of Topic</i> ” section of the report, is clear.	6 (100)	0	0
There is a need for a clinical practice guideline on this topic.	5 (83)	1 (17)	0
The literature search is relevant and complete.	5 (83)	0	0
The results of the trials described in the report are interpreted according to my understanding of the data.	6 (100)	0	0
The draft recommendations in this report are clear.	6 (100)	0	0
I agree with the draft recommendations as stated.	5 (83)	0	1 (17)
This report should be approved as a practice guideline.	3 (50)	1 (17)	0
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	<b>Very likely or likely</b>	<b>Unsure</b>	<b>Not at all likely or unlikely</b>
	4 (67)	1 (17)	0

NOTE: Some percentages do not add to 100 because of missing data.

### **Practice Guidelines Coordinating Committee Approval Process**

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Nine of eleven members of the PGCC returned ballots. Five PGCC members approved the practice guideline report as written, and four members approved the guideline conditional on the Systemic treatment DSG addressing specific concerns. PGCC members requested that the following issues be addressed prior to the approval of the guideline report: minor typographical errors and wording changes; more information on the differences between conventional and liposomal anthracyclines as well as an explicit description of the available evidence; a discussion of the importance of intermediate markers when important outcomes do not differ; and a more complete rationale for recommending, with qualifications, conventional anthracyclines as the preferred treatment option.

### **Modifications/Actions**

Based on the comments of the members of the PGCC, the Systemic Treatment DSG modified the practice guideline report to address the above issues. As a result, changes to the interpretive summary, recommendations, and qualifying statements were made.

## **IX. PRACTICE GUIDELINE**

These practice guideline recommendations reflect the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Systemic Treatment DSG and the Practice Guidelines Coordinating Committee.

### **Target Population**

These recommendations apply to patients with HIV-positive Kaposi’s sarcoma and good performance status (ECOG 0-2) who have progressive cutaneous disease despite prior treatment with interferon and/or vinblastine, or who have visceral disease that is symptomatic or progressive.

## **Recommendations**

- The use of conventional combination chemotherapy or single-agent liposomal anthracycline therapy, represent reasonable treatment options in the management of patients with HIV-positive Kaposi's sarcoma.

## **Qualifying Statements**

- Many anti-viral regimens used in the treatment of HIV cause peripheral nerve damage. In patients with HIV-positive Kaposi's sarcoma, the risk of neuropathic toxicity appears to be greater with vinca alkaloid-containing conventional treatment regimens than with single-agent liposomal anthracyclines. Therefore, if patients have neuropathy, or are at significant risk for neurotoxicity, liposomal anthracycline therapy may be preferable to conventional combination chemotherapy.

## **Future Research**

- Patients with HIV-positive Kaposi's sarcoma should be encouraged to enter clinical trials designed to test therapies aimed at improving survival and quality of life, trials designed to assess whether there are clinically important differences between the available liposomal anthracycline formulations and trials comparing single-agent liposomal anthracyclines with single-agent non-liposomal anthracyclines.
- More information is required to provide better estimates of the risk of cardiotoxicity from liposomal anthracyclines.

## **X. POLICY IMPLICATIONS**

Currently there is little information available about the number of patients who might be candidates for the liposomal anthracycline therapy. It is clear from reports in the literature and the experience of physicians involved in the care of these patients that the number of patients with HIV-positive Kaposi's sarcoma has decreased markedly in the last few years. This has generally paralleled the improvements in HIV therapy. The result is that there is a large pool of potential patients who might develop progressive HIV and associated diseases, including Kaposi's sarcoma. Consequently, the demand for the liposomal anthracycline agents, while at present likely to be limited, could expand if the incidence of progressive HIV and its related conditions were to rise. Additionally, the distribution of these patients may be uneven in various treatment centres around the province. In order to spread the burden of cost related to these agents in an equitable fashion, we believe reimbursement for these agents should be through the provincial program and be subject to meeting criteria for use. A community representative on the DSG strongly believed that the access to these agents should be through the provincial program.

Table 4 outlines the cost per week (in Canadian dollars) for treating an average patient with either a liposomal anthracycline regimen or a combination regimen of doxorubicin, bleomycin, and vincristine. The acquisition costs reflect only a component of the costs of delivering therapy. Costs associated with pharmacy workload and chemotherapy administration need to be considered, but are beyond the scope of this report. If liposomal anthracycline therapy is being considered, the direct cost of liposomal daunorubicin appears more attractive to that of liposomal doxorubicin. However, for an accurate comparison, detailed cost-effectiveness analyses based on Canadian data are needed. Unfortunately no such analyses were identified in the literature. Two cost-effectiveness analyses, one Swedish by Hjortsberg et al (14) and the other American by Bennett et al (15) were identified. The authors computed the projected cost (in American dollars) of the two liposomal formulations to achieve similar rates of response as reported in two of the identified randomized trials (4,9). The authors concluded that despite higher acquisition costs, the costs for liposomal doxorubicin were actually much lower than those for liposomal daunorubicin. Given the current price differences between the two liposomal

formulations, the results of the ongoing randomized trial (12) comparing the two formulations will hopefully clarify the relative merits of the two agents.

**Table 4. Cost per m<sup>2</sup> per week based on treating an average patient.**

Chemotherapeutic agent	Format	Acquisition cost	Dose schedule	Cost / cycle (for a person 1 m <sup>2</sup> )	Unit cost per week
liposomal doxorubicin	20 mg/ml	\$683.00	20 mg/m <sup>2</sup> every 3 weeks	\$683.00	\$227.67
liposomal daunorubicin	50 mg/20 ml	\$315.00	40 mg/m <sup>2</sup> every 2 weeks	\$252.00	\$126.00
doxorubicin	200 mg/100 ml	\$1019.48	20 mg/ m <sup>2</sup> every 2 weeks	\$101.95	\$50.98
bleomycin	15 U/ml	\$201.16	10 U /m <sup>2</sup> every 2 weeks	\$134.11	\$67.06
vincristine	5 mg/5 ml	\$84.50	1 mg every 2 weeks	\$16.90	\$8.45
ABV (combination of above three agents)					\$50.98 + \$67.06 + \$8.45 = \$126.49

NOTE: A = Adriamycin (doxorubicin); B = bleomycin; V = vincristine.

## XI. JOURNAL REFERENCE

Iscoe N, Bramwell V, Charette M, Oliver T, Zanke B. Liposomal anthracyclines in the management of patients with HIV-positive Kaposi sarcoma. *Curr Oncol* 2003;10(1):27-35.

## XII. ACKNOWLEDGMENTS

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*For a full list of members of the Breast Cancer Disease Site Group and the Practice Guidelines Coordinating Committee, please visit the CCO Web site at [http://www.cancercare.on.ca/access\\_PEBC.htm](http://www.cancercare.on.ca/access_PEBC.htm).*

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**Appendix 1: Staging classification for Kaposi's sarcoma.**

	<b>Good Risk (0) (All the following)</b>	<b>Poor Risk (1) (Any of the following)</b>
<b>Tumour (T)</b>	Confined to skin and/or lymph nodes and /or minimal oral disease*	Tumour-associated edema or ulceration Extensive oral KS Gastrointestinal KS KS in other non-nodal viscera
<b>Immune System (I)</b>	CD4 cells $\geq$ 200/ $\mu$ L	CD4 cells < 200/ $\mu$ L
<b>Systemic illness (S)</b>	No history of opportunistic infection or thrush No "B" symptoms** Performance status $\geq$ 70 (Karnofsky)	History of opportunistic infections and/or thrush "B" symptoms present Performance status < 70 Other HIV-related illness (e.g., neurological disease, lymphoma)

\* Minimal oral disease in non-nodular KS confined to the palate.

\*\* "B" symptoms are unexplained fever, night sweats, > 10% involuntary weight loss, or diarrhea persisting more than two weeks.

**Source:** Krown SE, Metroka C, Wernz JC for the AIDS Clinical Trials Group Oncology Committee. Kaposi's sarcoma in the acquired immune deficiency syndrome: A proposal for uniform evaluation, response, and staging criteria. *J Clin Oncol* 1989;7:1201-7.