Liposomal anthracyclines in the management of patients with HIV-positive Kaposi’s sarcoma

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CRD summary
This review assessed the effectiveness of liposomal anthracycline therapy in patients with human immunodeficiency virus-positive Kaposi’s sarcoma who have aggressive cutaneous or visceral disease. The authors concluded that liposomal therapy and conventional combination therapy represent equally valid approaches. Although the authors’ conclusions appear justified, potential biases in the review process may limit their reliability.

Authors’ objectives
To assess the effectiveness of liposomal anthracycline therapy in patients with human immunodeficiency virus (HIV)-positive Kaposi’s sarcoma who have aggressive cutaneous or visceral disease, in terms of survival, time to treatment failure, response rates, adverse effects and quality of life.

Searching
The authors originally searched MEDLINE (1966 to August 2002), Cancerlit (1983 to July 2002), the Cochrane Library (Issue 3, 2002), the PDQ clinical trials database, CMA Infobase and the National Guideline Clearinghouse; the search terms were reported. Conference proceedings from the meetings of the American Society of Clinical Oncology (1995 to 2002) and the European Society for Medical Oncology (1998 and 2000) were also searched and the reference lists of retrieved papers were checked. The search was updated by searching MEDLINE and EMBASE (from September 2002 to June 2004), the Cochrane Library (Issue 2, 2004), the PDQ clinical trials database, CMA Infobase and National Guidelines Clearinghouse. The authors also searched the conference proceedings from the meetings of the American Society of Clinical Oncology (2004) and the European Society for Medical Oncology (2002), reference lists and personal files to June 2004. Only studies published in the English language were included in the review.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for the review.

Specific interventions included in the review
Studies that compared a liposomal anthracycline regimen with observation, placebo or another chemotherapy regimen were eligible for the review. The included studies used liposomal daunorubicin or liposomal doxorubicin in the intervention group. The control regimens were doxorubicin, bleomycin and vincristine combination chemotherapy, vincristine and bleomycin combination therapy, or liposomal doxorubicin with bleomycin and vincristine.

Participants included in the review
Studies of patients with HIV-positive Kaposi's sarcoma with aggressive cutaneous or visceral disease were eligible for the review. The studies included patients with advanced-stage HIV-positive Kaposi's sarcoma or progressive HIV-positive Kaposi's sarcoma.

Outcomes assessed in the review
Studies that reported data on the outcomes of survival, time to treatment failure, response rates, adverse effects or quality of life were eligible for the review. All of the included studies reported data on survival, time to treatment failure, response rates and adverse effects. Two of the included studies reported data on quality of life.

How were decisions on the relevance of primary studies made?
The authors stated that studies were selected for review by a member of the Systemic Treatment Disease Site Group and methodologists. They did not state how any disagreements were resolved.
Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data were extracted on the patient and intervention characteristics and outcomes, presented as the number or proportion of events.

Methods of synthesis
How were the studies combined?
The authors stated that, owing to differences between the studies in treatment and control regimens, it was deemed inappropriate to combine the data using a meta-analysis. A narrative synthesis was presented.

How were differences between studies investigated?
Differences between the studies were described narratively. One study, which compared liposomal doxorubicin alone or in combination with bleomycin and vincristine, was described separately from the other three studies as the treatment regimen was not directly comparable with the other studies.

Results of the review
Four RCTs with a total of 860 participants were included in the review.

Survival, time to treatment failure and response rates.

There were no significant differences in median survival time or time to treatment failure between the treatment and control groups in any of the included studies. Two out of three studies found a statistically significant improved objective response rate in the groups receiving liposomal doxorubicin compared with the control groups (46% versus 25%, \( P < 0.001 \) and 59% versus 23%, \( P < 0.001 \)).

In the study that compared liposomal doxorubicin with liposomal doxorubicin combined with vincristine and bleomycin, there were no significant differences between the two groups in terms of survival, time to treatment failure or response rate.

Patients with visceral disease.

In one study, 45% of patients with visceral Kaposi's sarcoma who were randomised to receive liposomal daunorubicin showed an improvement in visceral disease, with 29% achieving a major response. In another study, 55% of patients with visceral Kaposi's sarcoma in the control group (receiving doxorubicin, bleomycin and vincristine) had documented evidence of improvement, with 33% achieving a major response. In another study, patients with visceral Kaposi's sarcoma had their incidence of symptomatic pulmonary Kaposi's sarcoma and symptomatic gastrointestinal Kaposi's sarcoma reduced with liposomal doxorubicin (reduction from 23% to 11%, \( P=0.002 \) and reduction from 16% to 4%, \( P=0.001 \), respectively). These symptoms were not reduced significantly with bleomycin and vincristine.

Adverse events.

In two studies, patients receiving doxorubicin, bleomycin and vincristine combination therapy experienced statistically significantly more alopecia and neuropathy than patients receiving liposomal daunorubicin (36% versus 8%, \( P<0.0001 \) and 41% versus 13%, \( P<0.0001 \), respectively) or liposomal doxorubicin (19% versus 1%, \( P<0.001 \) and 14% versus 6% \( P=0.002 \), respectively). Patients receiving doxorubicin, bleomycin and vincristine also experienced statistically significantly more nausea and/or vomiting than those receiving liposomal doxorubicin (34% versus 15%, \( P<0.001 \)). However, patients treated with liposomal daunorubicin had a statistically significantly higher incidence of grade 4 neutropenia than those receiving doxorubicin, bleomycin and vincristine (15% versus 5%, \( P=0.021 \)), while significantly more patients treated with liposomal doxorubicin suffered from mucositis than those receiving doxorubicin, bleomycin and vincristine (5% versus 2%, \( P=0.026 \)).
Paresthesia, peripheral neuropathy and constipation were statistically significantly more common in patients treated with bleomycin and vincristine than in those treated with liposomal doxorubicin (14% versus 3%, P<0.005, P<0.001 and 11% versus 2%, P<0.01, respectively). Grade 3 leucopenia, oral candidiasis and opportunistic infection were statistically significantly more common in patients treated with liposomal doxorubicin than in those treated with bleomycin and vincristine (72% versus 51%, P<0.001, 29% versus 18%, P<0.05 and 50% versus 30%, P<0.002, respectively).

In the study comparing liposomal doxorubicin with doxorubicin, bleomycin and vincristine combination therapy, statistically significantly less patients in the liposomal doxorubicin group discontinued treatment because of an adverse event (11% versus 37%, P<0.001). In the study comparing liposomal doxorubicin with bleomycin and vincristine combination therapy, less patients in the liposomal doxorubicin group withdrew from the study because of a chemotherapy-related event (11% versus 27%, P-value not stated).

Quality of life.

One study assessed quality of life and had end of treatment data available for over 70% of the treatment population. Patients receiving liposomal doxorubicin had statistically significantly better improvements from baseline to end of treatment, compared with patients receiving doxorubicin, bleomycin and vincristine, in four of the eleven domains assessed. Another study assessed quality of life, but end of treatment data were only available for a few patients. No statistically significant differences in quality-of-life scores were found at any of the time points measured.

Cost information

The authors reported the cost per week for treating an average patient was Can$227.67 with liposomal doxorubicin, Can$126.00 with liposomal daunorubicin and Can$126.49 with a combination regimen of doxorubicin, bleomycin and vincristine. However, they stated that the acquisition costs only reflect a component of the costs of delivering therapy; costs associated with pharmacy workload and chemotherapy administration should also be considered.

Authors' conclusions

Based on the limited evidence available, the use of liposomal therapy or conventional combination therapy represent equally valid approaches in the treatment of patients with HIV-positive Kaposi's sarcoma.

CRD commentary

The review question was clear in terms of the study design, participants, interventions and outcomes of interest. A number of relevant electronic databases were searched and the search terms were reported. Very little attempt was made to identify unpublished studies and language restrictions were applied, therefore relevant studies might have been missed. The authors stated that studies were selected for review by a member of the Systemic Treatment Disease Site Group and methodologists, thus reducing the potential for error or reviewer bias. However, they did not state how data were extracted for the review, and it was not therefore possible to assess the potential for reviewer bias or error for this part of the review process. The validity of the included studies was not assessed.

In view of the small number of studies identified, and the lack of a significant difference in median survival time or time to treatment failure between treatment groups, the authors' tentative conclusions appear justified. However, the potential for publication bias and the lack of a validity assessment reduce the reliability of these conclusions.

Implications of the review for practice and research

Practice: The authors stated that 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 who have good performance status, and who have progressive cutaneous disease despite prior treatment with interferon and/or vinblastine, or who have visceral disease that is symptomatic or progressive. They also stated that in patients with neuropathy, or patients who are at significant risk for neurotoxicity, liposomal anthracycline therapy may be preferable to conventional combination chemotherapy. In addition, patients should be informed of the harms and
benefits associated with each treatment regimen, and patient preferences should be considered when making treatment decisions.

Research: The authors stated that 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 test differences between different liposomal anthracycline formulations, and trials comparing single-agent liposomal anthracyclines with single-agent non-liposomal anthracyclines. They also stated that further information is required to better estimate the risk of cardiotoxicity from liposomal anthracyclines.

Bibliographic details

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