Pharmacotherapeutic value and cost-effectiveness of pegylated liposomal doxorubicine and paclitaxel for the treatment of AIDS-related Kaposi's sarcoma

Review on pegylated liposomal doxorubicine and paclitaxel in AIDS-related Kaposi's sarcoma for ZonMw

Christel C.L.M. Boons, MSc[1], Maurits W. van Tulder, PhD[2,3], Cordula Wagner, PhD[4,5], Jacqueline G. Hugtenburg, PhD[1,6]

[1] Department of Clinical Pharmacology and Pharmacy, VU University Medical Center, Amsterdam
[2] Department of Epidemiology & Biostatistics & EMGO-Institute for Health and Care Research, VU University Medical Center, Amsterdam
[3] Department of Health Sciences & EMGO Institute for Health and Care Research, VU University, Amsterdam
[4] Department of Public and Occupational Health, VU University Medical Center, Amsterdam
[5] NIVEL, Utrecht
[6] EMGO[+] Institute for Health and Care Research, VU University Medical Center, Amsterdam

Date: March, 2011

SUMMARY [Dutch]

Introductie
Kaposi sarcoom (KS) is een zelden voorkomende kanker waarbij abnormale groei onder de huid, om de mond, neus, keel en andere organen optreedt. De tumor wordt veroorzaakt door het herpesvirus 8. De meest voorkomende vorm is de AIDS-gerelateerde vorm.
Verondersteld wordt dat immuunsuppressie een rol speelt bij de ontwikkeling van KS.
Tot de jaren 80 kwam KS nog vrij veel voor. Echter, de ontwikkeling van highly active antiretroviral therapy (HAART) heeft geleid tot een drastische afname van de incidentie. In 2008 waren er 58 nieuwe gevallen van KS, 50 mannen en 8 vrouwen.
In dit review wordt de literatuur over de werkzaamheid, effectiviteit, veiligheid, kwaliteit van leven en de kosten-effectiviteit van chemotherapie bij eerste- en tweedelijnsbehandeling van KS samengevat. Hierbij wordt de behandeling ook belicht vanuit het perspectief van de patiënt, de medisch oncoloog en de apotheker.

Methode
In de databases MEDLINE, EMBASE en Cochrane is met trefwoorden gezocht naar reviews van gerandomiseerde klinische trials (RCTs) en economische evaluaties van de behandeling van KS met gepegyleerd liposomaal doxorubicine (PLD) en paclitaxel (PAC). Tevens is met trefwoorden gezocht of na het verschijnen van de meest recente review nog nieuwe onderzoeken zijn gepubliceerd.
Een vertegenwoordiger van de patiëntenvereniging en één medisch oncoloog met ervaring met de behandeling van KS zijn geïnterviewd. Hierbij zijn vragen gesteld over de behandeling van KS, de toxiciteit van de behandeling en de voorlichting bij het maken van keuzes omtrent de behandeling.

Resultaten
Er zijn twee fase III onderzoeken waarin de werkzaamheid, toxiciteit en kwaliteit van leven van eerstelijnsbehandeling van KS met PLD is vergeleken met doxorubicine, bleomycine en vincristine (ABV). Er is één onderzoek waarbij PLD is vergeleken met liposomaal daunorubicine en er is één onderzoek waarbij PLD is vergeleken met PAC.
De werkzaamheid van PLD was vergelijkbaar met ABV, maar PLD werd beter verdragen en de kwaliteit van leven van met PLD behandelde patiënten was beter. PLD leek beter dan daunorubicine. PLD was even werkzaam als PAC, maar het toxiciteitsprofiel van PLD was gunstiger. Het toevoegen van antikankermiddelen aan PLD heeft niet geleid tot een betere werkzaamheid.

De fase III onderzoeken waarin PLD is vergeleken met ABV en daunorubicine zijn uitgevoerd in de periode voor de ontwikkeling van HAART, wat op zich al tot een verbetering van de symptomen van KS heeft geleid. PLD is daarom in combinatie met HAART mogelijk beter werkzaam dan PLD alleen.
In één onderzoek was ook de kwaliteit van leven onderzocht. PLD leidde tot een grotere verbetering van de kwaliteit van leven dan ABV.
Er zijn enkele beperkte onderzoeken van de kosten-effectiviteit van PLD verricht. Hieruit is gebleken dat de kosten-effectiviteit van PLD beter is dan dat van ABV of daunorubicine.
Laag gedoseerd PAC is onderzocht in fase II onderzoeken in de tweedelijnsbehandeling van KS. In de met chemotherapie voorbehandelde patiënten was PAC werkzaam en de resultaten van één van de onderzoeken liet een verbetering van de kwaliteit van leven zien.
Er is naar deze behandeling geen farmacoeconomisch onderzoek verricht.

Conclusie

Geconcludeerd kan worden dat de werkzaamheid, veiligheid en kwaliteit van leven van de eerstelijnsbehandeling met PLD in KS goed is onderbouwd. PLD is een effectieve behandeling, waarvan de kosten acceptabel zijn. Er is beperkt onderzoek van de kosten-effectiviteit. De werkzaamheid, veiligheid en kwaliteit van leven van de behandeling met PAC in de tweede lijn is met beperkte gegevens onderbouwd. Er is geen farmacoeconomisch onderzoek van deze behandeling verricht. Gezien de geringe omvang van het voorkomen van KS, de gunstige resultaten van de behandeling met PLD en het lage kostenbeslag is het niet zinvol om meer farmacoeconomisch onderzoek te verrichten.

INTRODUCTION

Type of disease

Kaposi's sarcoma (KS) is a rare cancer that develops from the cells that line lymph or blood vessels. It causes abnormal tissue to grow under the skin, in the lining of the mouth, nose, and throat or in other organs. The tumour is caused by the human herpesvirus 8 (HHV8). The different types of KS are defined by the different populations it develops in. The most common type is AIDS-related KS. This type develops in people who are infected with HIV. The exact cause of KS is unknown, but the disease may be related to immunosuppression. Genetic or hereditary predisposition is also suspected. In people with AIDS, KS is caused by an interaction between the human immunodeficiency virus (HIV), immune system suppression, and human herpesvirus-8 (HHV-8). Occurrence has been linked with sexual transmission of HIV and HHV-8. The 5-year survival rate in the Netherlands is 72% (1).

Epidemiology

KS was once a common cancer among people living with AIDS in the 1980s. In the past 20 years the incidence of AIDS-related KS decreased dramatically in developed countries because of the widespread implementation of highly active antiretroviral therapy (HAART) in the late 1990s. It has also been suggested that safer sexual practices among homosexual men may have led to reduced transmission of HHV-8. The use of more effective antiretroviral treatments is associated with a reduction in immunodeficiency and may have resulted in a more effective immune response to HHV-8. The age standardised incidence and mortality rates (ESR) of KS in the Netherlands decreased from 0.6 per 100,000 population in 1989 to 0.3 in 2008 (1). In 2008 almost 60 new cases with KS were diagnosed in the Netherlands. The incidence is higher in Dutch men compared to Dutch women, in 2008 approximately 50 men were diagnosed with KS (ESR 0.5) and 8 women (ESR 0.1).

Licensed chemotherapy for KS

KS is treated with chemotherapy. Pegylated liposomal doxorubicin (PLD) and paclitaxel (PAC) are active cytotoxic agents for the treatment of AIDS-related KS.

The present review includes PLD and PAC which are registered on the 'Beleidsregel dure geneesmiddelen in ziekenhuizen' as expensive medicine. PLD has been licensed in the Netherlands since 1996 for the treatment of AIDS-related KS in patients with AIDS who have very damaged immune systems and extensive sarcoma on the skin, the moist body surfaces or the internal organs. PLD is also licensed for the treatment of other malignancies, including breast cancer, multiple myeloma, and ovarian cancer. PLD infusion contains the active ingredient doxorubicin hydrochloride. In PLD doxorubicin molecules are encapsulated in a

bilayer sphere of pegylated lipids called liposomes. The effect of doxorubicin is based on the inhibition of DNA, RNA and protein synthesis. The recommended dose for PLD as the treatment of KS is 20 mg/m2, administered every two to three weeks for two to three months. PAC has been licensed in the Netherlands since 1993 for the second-line treatment of advanced AIDS-related KS, when treatment with another type of anticancer medicine has failed. PAC is also indicated for other malignancies, including breast cancer, non-small cell lung cancer, and ovarian cancer. PAC is a cytostatic agent that prevents cell division by promoting disassembly of microtubules. PAC stabilizes microtubules and as a result, interferes with the normal breakdown of microtubules during cell division. In the presence of this drug, cancer cells become clogged with microtubules resulting in a mitotic arrest. The recommended dose for second-line treatment for AIDS-related KS includes 100 mg/m2, administered in a 3-hour infusion every 2 weeks.

Objective

A systematic review of the recent literature on treatment with the ‘expensive’ medicine in AIDS-related Kaposi’s sarcoma (KS) was performed. The objectives for the review were to evaluate the pharmacotherapeutic value and cost-effectiveness of pegylated liposomal doxorubicin (PLD) and paclitaxel (PAC) for the treatment of AIDS-related KS and to evaluate the impact on quality of life.

METHODS

Search strategy

A search was performed by an experienced librarian using the MEDLINE, EMBASE and Cochrane databases. The search strategies, based on terms on KS, PLD and/or PAC and either randomised clinical trial (RCT) or economic evaluations, are presented in Appendix A. The search included both Medical Subject Headings (MeSH) terms, e.g. "Sarcoma, Kaposi", as well as text words. The search strategy was adapted accordingly for the EMBASE and Cochrane databases.

Selection criteria

Selection criteria that were used to include studies:

- Systematic reviews (and RCTs and economic evaluations if published after inclusion date for studies in the review)
- Patients with AIDS-related KS
- Treatment with PLD and/or PAC

Criteria for considering studies for inclusion

Systematic reviews that investigated the pharmacotherapeutic value and cost-effectiveness of PLD and/or PAC for the treatment of AIDS-related KS were included. Additional phase III RCTs and economic evaluations published after the publication date of the most recently performed reviews were also included. Inclusion criteria for economic evaluations were cost-effectiveness analysis, cost-utility analysis and cost-minimisation analysis.

Type of studies included

Participants

Studies that included patients with AIDS-related KS were included.

Type of intervention

Treatment with PLD and PAC, used alone or in combination with other chemotherapeutic therapy, were eligible for inclusion.

Data collection and analysis

Two reviewers (JH and CB) independently evaluated all titles and abstracts. To streamline the data collection process, all references were exported and managed using Reference Manager, Version 11 (Thomson ISI ResearchSoft, Berkeley, CA, USA). Full paper manuscripts of potentially relevant titles/abstracts were obtained and assessed for inclusion.

Studies that did not fulfil all criteria were excluded. Disagreements were resolved by discussion until consensus was reached.

Outcomes

Data on the following outcome measures were eligible for inclusion in this review:

- Efficacy, effectiveness, toxicity, and quality of life is based on a systematic search of the literature on RCTs.
- Ongoing clinical trials on KS were searched on the Clinical Trials Registry of the U.S. National Library of Medicine (www.clinicaltrials.org, accessed February 2011) and the Dutch Trial Registry (www.trialregister.nl, accessed February 2011).
- No guidelines for the treatment of KS are available.
- Daily clinical practice includes an interview with one dedicated oncologist, dispension data of a hospital pharmacy of an academic medical centre in the Netherlands, and input of the patients association.
- Data on generic products are retrieved from the Dutch Medicines Evaluation Board (CBG).
- Data on costs are retrieved from the Dutch Foundation for Pharmaceutical Statistics (SFK).
- Economic evaluation is based on a systematic search of the literature including cost-effectiveness analysis and cost-utility analysis.

RESULTS

REVIEW OF PHARMACOTHERAPEUTIC VALUE

In total 353 publications were identified. Of these 353 publications, one systematic review (2) and two randomised clinical trials (3;4) on the effectiveness of PLD in the treatment of AIDS-related KS were identified. In addition, one review was identified addressing studies of the effectiveness of both PLD and PAC on AIDS-related KS (5). The results are summarized in Table 1.

First-line treatment

Two randomised controlled trials of PLD are described in the reviews of Cattelan et al (5) and Di Trolio (2). In the first phase III study 258 chemotherapy naïve patients with advanced AIDS-related KS were randomly assigned to receive either PLD (20 mg/m2) or the combination of doxorubicin (20 mg/m2), bleomycin (10 mg/m2) and vincristine (1 mg) (ABV) every two weeks for six cycles (6). This study was also included in the systematic review of Di Trolio et al. Among 133 patients randomized to receive PLD, one achieved a complete clinical response and 60 achieved a partial response for an overall response rate (ORR) of 45.9%. Among 125 patients randomized to receive ABV, 31 achieved a partial response (24.8%). The difference was significant ($p < 0.001$).
In the second phase III study, PLD (20 mg/m2) was compared with a combination of bleomycin (15 IU/m2) and vincristine (2 mg) (BV) in 241 patients with AIDS-related KS (7). Both regimens were administered by intravenous infusion every 3 weeks for six cycles. The RR to PLD was superior to BV: 58.7% versus 23.3% ($p < 0.001$).

In the randomised phase III trial described by Cooley et al. patients were randomised in a ratio 3:1 to either PLD (20 mg/m2; n = 60) or liposomal daunorubicin (40 mg/m2; n = 19). The results of this trial were published in its final form by Cooley et al (2007) (4). Clinical benefit was observed in 48/60 patients (80%) receiving PLD and was maintained for a median of 62 days (range: 28-107 days). Clinical benefit was achieved by 12/19 patients (63.2%) receiving liposomal daunorubicin and was maintained for a median of 55 days (range: 28-84 days). Tumor responses were achieved by 55.0% of patients receiving PLD and 31.6% of patients receiving liposomal daunorubicin.

The review of Di Trolio also included one study designed to determine whether additional agents may improve the efficacy of PLD (8). In a randomised trial involving 126 patients it has been shown that the addition of BV did not result in additional benefits.

Table 1 : Studies on first-line treatment in KS

Study	n	Drug	ORR (%)	Rate of termination due to AE (%)
Northfelt et al. 1998	133	PLD	45.9	NA
	125	ABV	24.8	NA
Stewart et al. 1999	121	PLD	58.7	26.7
	120	BV	23.3	10.7
Cooley et al. 2007	60	PLD	55.0	NA
	19	liposomal daunorubicin	31.6	NA

Abbreviations: PLD=pegylated liposomal doxorubicin; ABV= doxorubicin/bleomycin/vincristine; BV= bleomycin/vincristine; ORR=overall response rate; AE=adverse event.

Second-line treatment

Cattelan et al. described three phase II studies of PAC in patients with AIDS-related KS who failed on treatment with liposomal anthracycline therapy (5). A study of Welles et al. included 29 patients treated with PAC 135 mg/m2, every 3 weeks, which was escalated to a maximum of 175 mg/m2 (9). A study of Gills et al. evaluated a new dosage schedule of 100 mg/m2 two weeks (10). In these studies the tumour response varied from 59 to 71% and the median duration of response was 10 months. In a more recent trial of Tulpule et al. the effectiveness of PAC 100mg/m2 was studied in second-line treatment of 107 patients with AIDS-related KS (11). First-line treatment could include ABV, liposomal daunorubicin of PLD. The use of protease inhibitor bases antiretroviral treatment was permitted. The ORR was 56%, with a median duration of response of 8.9 months.

TOXICITY

Di Trolio et al summarised the toxicity data of the studies of Northfelt et al. and Stewart et al. (6;7). Compared with ABV treatment or BV, PLD was associated with a reduced incidence of nausea/vomiting and alopecia and neuropathy. As compared to ABV, myelosuppression and fever were less sever with PLD. However, the incidence of infection was not lower. In the comparison with BV, PLD was more myelosuppressive. Hand-foot syndrome was uncommon with the doses and schedules of PLD used in these studies. Mucositis, stomatitis and

infusion reactions such as dyspnea and hypotension occurred more frequently in patients treated with PLD.
In the study of Cooley et al. patients treated with PLD (20 mg/m2) experienced neutropenia (30%), nausea (28.3%), and asthenia (16.7%) (4). These incidence were similar to the findings of the studies described in the review of Di Trollio.

PAC was generally well tolerated. However, 87%, 100% and 66% of the patients in the studies of Gill et al. (10), Welles et al. (9) and Tulpule et al. (11) reported to have alopecia. And 61% and 83% of cases had bone marrow suppression. Grade 4 neutropenia was seen in 35% of the patients in the study of Tupule et al.

QUALITY OF LIFE

The study of Northfelt also addressed the quality of life under treatment of PLD. There was a significant difference between PLD and ABV in four domains: general health, social functioning, energy and fatigue. In more patients in the PLD group than in the ABV group a clinical significant improvement, defined as a change of more than 10 points on the quality of life score (65% vs. 43%, p = 0.008). The duration of change was longer in PLD treated patients than in ABV treated patients.

Tulpule et al. reported significant improvements in quality of life of patients treated with second-line treatment with PAC 110 mg/m2 (11). KS related symptoms as facial disease, tumour related edema and pulmonary involvement significantly improved.

ONGOING PHASE III TRIALS

No phase III trials on the treatment of KS are currently conducted.

REVIEW OF GUIDELINES

Treatment guidelines for the treatment of AIDS-related sarcoma are not available.

DAILY CLINICAL PRACTICE

Structured interview

One medical oncologist from an academic medical centre in Amsterdam, the Netherlands, was invited to participate in a structured interview. The items discussed were the number of patients with KS, treatment regimens used for KS, treatment and prevention of toxicity, participation in studies, and means of informing and counselling patients. The total number of new patients with KS in this hospital is approximately 1 per year.

According to the oncologist, all patients receive PLD as first-line treatment, 20 mg/m2 administered every 4 weeks until remission of the disease. For patients relapsing after first-line treatment and requiring second-line treatment, PLD may be considered again depending on the progression-free interval. BV is considered as a good alternative. The oncologist reported that taxanes are never used.

No toxicities are experienced by AIDS-related KS treated with PLD. In addition, no hospital admission are reported due to PLD associated toxicity and no prevention methods are needed.

The interviewed medical oncologist reported not to know of any guidelines available for the treatment of KS. According to the medical oncologist it is not worthwhile to develop guidelines because of the low incidence of the disease and the well documented treatment with low dose PLD.

According to the oncologist, no trials on the treatment of KS are currently conducted.

Input of patients' association

A representative of the HIV patients' association was invited to participate in a structured interview.
The incidence rates of KS has decreased dramatically due to new effective combination therapy. Therefore, the representative of the HIV patients' association reported to have a poor view of the current status of treatment of AIDS-related KS and the associated information process. The representative of the HIV patients' association believes that it is important that treatment is evidence based. However, it is difficult to develop and study new treatments because of the rarity of AIDS-related KS in the developed world.
Generally the representative of the HIV patients' association believes that patients are not aware of the costs of the treatment offered. In addition, no concerns about the availability of

treatment are experienced by patients. Regardless of the actual costs of treatment, in relation to the number of patients with AIDS-related KS the total costs are expected to be minimal. If patients were experiencing problems with the availability of treatment, than the HIV patients' association would play a role in resolving this problem.

Illustration of pharmacy dispension data

Due to the low incidence rate of KS, it was not possible to provide an illustration based on dispension data of the hospital pharmacy of one academic medical centre. In 2009-2010, only one patient with KS was treated at the department of internal medicine. This patient received standard first-line treatment for AIDS-related KS including PLD 20 mg/m2, administered every 3 weeks. This was changed to PAC 80 mg/m2, administered every 2 weeks.

GENERIC PRODUCTS

PAC was discovered in 1967 in a U.S. National Cancer Institute program at the Research Triangle Institute in North Carolina. It was isolated from the bark of the Pacific yew tree, Taxus brevifolia. It was named Taxol. When it was developed commercially by Bristol-Myers Squibb (BMS) the generic name was changed to PAC and the BMS compound was sold under the trademark Taxol® (12). It has been licensed in the Netherlands in 1993 (13) and since then several generic versions were developed (Table 2).

Table 2 : Generic products of PAC

Name	Authorisation date	Marketing Authorisation Holder
Taxol	20-9-1993	Bristol-Myers Squibb B.V.
Paxene	19-7-1999	Norton Healthcare Ltd.
Paclitaxin	5-11-2004	Pharmachemie B.V.
Paclitaxel	26-1-2005	Pharmachemie B.V.
Paclitaxel Hospira	13-9-2005	Hospira Benelux BVBA (B)
Paclitaxel CF	9-10-2006	Centrafarm B.V.
Paclitaxel Sandoz	19-6-2007	Sandoz B.V.
Paclitaxel Mylan	12-7-2007	Mylan B.V.
Paclitaxel Stragen	3-9-2007	Stragen Nordic A/S (D)
Paclitaxel Actavis	20-6-2008	Actavis Group PTC ehf (IS)
Paclitaxel Allgen	29-4-2009	ALL-GEN Pharmaceuticals & Generics BV
Paclitaxel Fresenius Kabi	6-8-2009	Fresenius Kabi Nederland B.V. (B)
Paclitaxel Dr. Schlichtiger	3-12-2009	Dr. Schlichtiger GmbH (G)
Paclitaxel Accord	31-8-2010	Accord Healthcare B.V.

Doxorubicin was originally isolated in the 1950's by an Italian research company, Farmitalia Research Laboratories, from bacteria found in soil samples taken from the area surrounding a 13th century castle in Italy. Researchers discovered that changes in biological activity could be made by minor changes in the structure of the compound. A strain of Streptomyces was mutated and produced a different, red-colored antibiotic (14). Doxil (outside the United States known as Caelyx) is a pegylated liposome-encapsulated form of doxorubicin made by Ben Venue Laboratories for Johnson & Johnson in the United States. Caelyx is marketed by Schering-Plough only and has been licensed in the Netherlands in 1996 (13).

COSTS

Since 1990, the Dutch Foundation for Pharmaceutical Statistics (SFK) has been collecting and analyzing exhaustive data about the use of pharmaceuticals in the Netherlands. The expenditure increase can primarily be traced back to the increasing use of ‘expensive’ medicines. Along with the increasing use of expensive medicines, the expenditures grew because of a substantial nationwide growth in the number of prescriptions (15). In 2008 in the Netherlands, the total costs of expensive medicines for the treatment of cancer were € 94.3 million, slightly higher than in 2007 when the total costs were € 90.4 million. PAC was the first expensive drug for which a special financial arrangement was made. Since 2002, PAC has been registered as ‘expensive’ medicine. Several generic preparations are available. Until 2007, a vial containing 300 mg of PAC infusion concentrate was approximately € 1,800 and declined to € 960 in 2010 (16). Total cost of PAC decreased from € 13,9 million in 2004 to € 5,3 million in 2008. It is very likely that the patent process is a major cause of these lower costs. PLD is registered as ‘expensive’ medicine since 2004. The total costs of PLD have been increasing from € 2.1 million in 2004 to € 6.5 million in 2008 (15). In 2010 the costs were €431 per 10 mg vial and €1.080 per 50 mg vial (16).

These numbers represent the overall costs of PAC and PLD including all indications. No data are available to estimate what part of the total costs per drug is contributed to the treatment of AIDS-related KS.

REVIEW OF ECONOMIC EVALUATIONS

In total 16 publications were identified. Of these 16 publications, one review was identified (17) on the cost-effectiveness of PLD for the treatment of AIDS-related KS. In addition, one

more recent study by Vanni et al. examined the cost-effectiveness of KS chemotherapy regimens in Brazil (18). No pharmacoeconomic assessments have been performed in order to determine whether treatment with PAC is cost effective in the treatment of KS.
All figures were recalculated to Euros and corrected for 4% inflation per year from the year of publication till 2011. The results of the economic evaluation are summarized in Table 3.

A review by Bennett et al (2004) examined the cost-effectiveness of PLD for the treatment of KS (17;19). Two articles were included (20;21).
In 1998, Bennett and colleagues conducted an indirect comparison based on clinical trial data of two separate, randomized phase III studies comparing PLD with BV (7) and liposomal daunorubicin with conventional ABV (22). The cost per cycle for treatment with PLD was more than twice as high as for liposomal daunorubicin. However, the mean number of cycles and the dose and length of cycles for liposomal daunorubicin were almost twice those for PLD. Despite the higher costs for PLD, the total cost of treatment for KS and chemotherapy-related hematologic toxicities per patient were almost similar (€ 6662 for PLD vs. € 6243 for liposomal daunorubicin; incremental cost was € 420). RR were 59% for PLD and 25% for liposomal daunorubicin. As a result, the incremental cost-effectiveness ratio (ICER), defined as average costs per responder, for PLD was less than half compared to treatment with liposomal daunorubicin. The ICER per additional responder for PLD was € 1233 compared to liposomal daunorubicin.
In 1999, Hjortsberg and colleagues conducted a retrospective economic evaluation comparing PLD with liposomal daunorubicin, using the same clinical trial data and analysis methods as Bennett and colleagues. The cost per objective response was € 17,291 for liposomal daunorubicin and € 8364 for PLD. The ICER to achieve one responder was € 1801, using PLD instead of liposomal daunorubicin.
Sensitivity analysis in each of the studies included showed that PLD was consistently cost-effective for the treatment of KS. Bennett and colleagues concluded that the overall cost to achieve objective response was substantially lower with PLD than with liposomal daunorubicin.

A more recent study from Brazil by Vanni et al examined the cost-effectiveness of KS chemotherapy regimens in Brazil (18;19). They developed a decision-analysis model. Effectiveness data were derived from randomized phase III trials evaluating PLD, liposomal daunorubicin, and the ABV regimen. Resource data on direct medical costs were obtained from local sources. Total cost per patient for PLD is € 3991 and for liposomal daunorubicin is € 3433. The difference between costs was mainly related to the different mean number of treatment cycles used (5.2 cycles vs. 8.6 cycles), which was compensated for by the higher

acquisition cost per cycle for PLD compared to liposomal daunorubicin (€ 744 vs. € 383). Nonetheless, cost-effectiveness estimates favoured PLD compared with liposomal daunorubicin (€ 8954 vs. € 14,176 per responder), reflecting the higher RR reported with PLD (46% vs. 25%). The ICER for PLD compared to liposomal daunorubicin was € 2654. At difference with previous reports, this study showed that ABV was the most rational treatment option in a resource-limited country like Brazil. ABV showed better results when compared to both PLD (€ 1106 vs. € 8953) and liposomal daunorubicin (€ 1106 vs. € 14,174). The ICER per additional responder of using PLD instead of ABV was € 18,297.

In summary, results showed that the overall cost to achieve objective response was substantially lower with PLD compared to liposomal daunorubicin. In a resource-limited country like Brazil, ABV treatment seems to be the most reasonable treatment option for AIDS-related KS.

Table 3 : Results of economic evaluation on PEM for the treatment of AIDS-related KS

Study	Type of economic evaluation	Perspective used	Time frame	Unit cost data	Source of effectiveness data	Source of resource use data	Intervention	RR (%)	Total costs	Cost-effectiveness (ICER)
Bennett et al. 1998	Decision-analysis model	US	NA	Direct medical costs	Stewart et al. 1998 Gill et al. 1996	Local sources	PLD liposomal daunorubicin	59 25	€ 6662 € 6243	€ 1233 / additional responder
Hjortsberg et al. 1996	Retrospective economic evaluation	Sweden	NA	Direct medical costs	Stewart et al. 1998 Gill et al. 1996	Local sources	PLD liposomal daunorubicin	59 25	€ 8364 / response € 17,291 / response	€ 1801 / additional responder
Vanni et al. 2007	Decision-analysis model	Brazil	NA	Direct medical costs	Northfelt et al. 1998 Gill et al. 1996	Local sources	PLD liposomal daunorubicin ABV (PLD control group)	46 25 25	€ 3991 € 3433 € 268	€ 2654 [a] / additional responder € 18,297 [b] / additional responder

Abbreviations: PLD=pegylated liposomal doxorubicin; ABV=doxorubicin/bleomycin/vincristine; RR=response rate; ICER=incremental cost-effectiveness ratio; NA=not available.

[a] Comparing PLD with liposomal daunorubicin.

[b] Comparing PLD with ABV.

DISCUSSION AND CONCLUSION

Two phase III trials on the efficacy, effectiveness, safety and quality of life of low dose of PLD compared with ABV and in one trial PLD was compared with liposomal daunorubicin. The results of these studies showed that PLD offers comparable efficacy and effectiveness, but better tolerability and quality of life as compared to ABV and seemed more effective than daunorubicin. Studies on the effectiveness of the addition of other therapeutic drugs to PLD did not result in an improved effectiveness. The phase III studies, investigating the effectiveness of PLD were generally performed before the development of HAART, which, as such has been shown to dramatically reduce the symptoms of KS. It is therefore very likely that combined HAART with PLD is more effective than PLD alone. One study also addressed the quality of life and showed that treatment with PLD was accompanied by a better quality of life than treatment with ABV.

Low dose PAC is studied in the second-line treatment of KS three phase II studies. Even in pretreated patients, this drug has shown activity and one of the studies also showed an improvement of quality of life.

Studies on the cost-effectiveness of PLD in first-line treatment for the Swedish and US situation show that PLD was more cost-effective than ABV or daunorubicin. One study for the situation in Brazil concluded that PLD treatment was too expensive for a country as Brazil. It could be possible that different circumstances with respect to the possibilities of the organisation of health care in a third world country may lead to a lower quality of treatment of toxicity and thereby lower costs of treatment. It is also possible that treatment costs of two treatments compared are differentially influenced by the cost of health care givers.

Guidelines on the treatment of KS are not available. According to the medical oncologist interviewed by the authors it is not worthwhile to develop guidelines because of the low incidence of the disease and the well documented treatment with low dose PLD.

It can be concluded that low dose PLD is an effective treatment for KS, a seldomly occurring disease as the result of HAART. Cost of treatment seems acceptable.

REFERENCES

(1) Kanker in Nederland. Incidentie. Vereniging van Integrale Kankercentra 2010 June 22Available from: URL: http://www.ikcnet.nl/page.php?id=114

(2) Di Trolio R, Di Lorenzo G, Delfino M, De Placido S. Role of pegylated lyposomal doxorubicin (PLD) in systemic Kaposi's sarcoma: a systematic review. Int J Immunopathol Pharmacol 2006;19:253-63.

(3) Cianfrocca M, Lee S, Von Roenn J, Tulpule A, Dezube BJ, Aboulafia DM, et al. Randomized trial of paclitaxel versus pegylated liposomal doxorubicin for advanced human immunodeficiency virus-associated Kaposi sarcoma: evidence of symptom palliation from chemotherapy. Cancer 2010;116:3969-77.

(4) Cooley T, Henry D, Tonda M, Sun S, O'Connell M, Rackoff W. A randomized, double-blind study of pegylated liposomal doxorubicin for the treatment of AIDS-related Kaposi's sarcoma. Oncologist 2007;12:114-23.

(5) Cattelan AM, Trevenzoli M, Aversa SML. Novel pharmacological therapies for the treatment of AIDS-related Kaposi's sarcoma. Expert Opin Investig Drugs 2004;13:501-13.

(6) Northfelt DW, Dezube BJ, Thommes JA, Miller BJ, Fischl MA, Friedman-Kien A, et al. Pegylated-liposomal doxorubicin versus doxorubicin, bleomycin, and vincristine in the treatment of AIDS-related Kaposi's sarcoma: results of a randomized phase III clinical trial. J Clin Oncol 1998;16:2445-51.

(7) Stewart S, Jablonowski H, Goebel FD, Arasteh K, Spittle M, Rios A, et al. Randomized comparative trial of pegylated liposomal doxorubicin versus bleomycin and vincristine in the treatment of AIDS-related Kaposi's sarcoma. International Pegylated Liposomal Doxorubicin Study Group. J Clin Oncol 1998;16:683-91.

(8) Mitsuyasu RT, von Roenn J, Krown S, Kaplan L, Testa M. Comparison study of liposomal doxorubicin (DOX) alone or with bleomycin and vincristine (DBV) for treatment of advanced AIDS-associated Kaposi's sarcoma (AIDS-KS): AIDS Clinical Trial Group (ACTG) protocol 286 (Meeting abstract). 1997.

(9) Welles L, Saville MW, Lietzau J, Pluda JM, Wyvill KM, Feuerstein I, et al. Phase II trial with dose titration of paclitaxel for the therapy of human immunodeficiency virus-associated Kaposi's sarcoma. J Clin Oncol 1998;16:1112-21.

(10) Gill PS, Tulpule A, Espina BM, Cabriales S, Bresnahan J, Ilaw M, et al. Paclitaxel is safe and effective in the treatment of advanced AIDS-related Kaposi's sarcoma. J Clin Oncol 1999;17:1876-83.

(11) Tulpule A, Groopman J, Saville MW, Harrington W, Jr., Friedman-Kien A, Espina BM, et al. Multicenter trial of low-dose paclitaxel in patients with advanced AIDS-related Kaposi sarcoma. Cancer 2002;95:147-54.

(12) Paclitaxel. From Wikipedia, the free encyclopedia. Wikimedia Foundation, Inc 2011 February 21Available from: URL: http://en.wikipedia.org/wiki/Paclitaxel

(13) Database Human Medicines. Medicines Evaluation Board 2011 March 2Available from: URL: http://www.cbg-meb.nl/cbg/nl

(14) Doxorubicin. From Wikipedia, the free encyclopedia. Wikimedia Foundation, Inc 2011 February 18Available from: URL: http://en.wikipedia.org/wiki/Doxorubicin

(15) Monitor Dure Geneesmiddelen 2008. Kosten van dure- en weesgeneesmiddelen in het ziekenhuis. Den Haag: Stichting Farmaceutische Kengetallen; 2010.

(16) Farmacotherapeutisch Kompas 2010. Onafhankelijke geneesmiddelinformatie voor professionals in de zorg. Amstelveen: College voor Zorgverzekeringen 2011 January 1Available from: URL: http://www.fk.cvz.nl

(17) Bennett CL, Calhoun EA. Pharmacoeconomics of liposomal anthracycline therapy. Semin Oncol 2004;31:191-5.

(18) Vanni T, Fonseca BAL, Polanczyk CA. Cost-effectiveness analysis comparing chemotherapy regimens in the treatment of AIDS-related Kaposi's sarcoma in Brazil. HIV Clin Trials 2006;7:194-202.

(19) Cainelli F, Vallone A. Safety and efficacy of pegylated liposomal doxorubicin in HIV-associated Kaposi's sarcoma. Biologics 2009;3:385-90.

(20) Bennett CL, Golub RM, Stinson TJ, Aboulafia DM, von Roenn J, Bogner J, et al. Cost-effectiveness analysis comparing liposomal anthracyclines in the treatment of AIDS-related Kaposi's sarcoma. J Acquir Immune Defic Syndr Hum Retrovirol 1998;18:460-5.

(21) Hjortsberg C, Persson U, Lidbrink E, Bennett C. Cost-effectiveness analysis of pegylated-liposomal doxorubicin and liposomal daunorubicin treatments in patients with Kaposi's sarcoma. Acta Oncol 1999;38:1063-7.

(22) Gill PS, Wernz J, Scadden DT, Cohen P, Mukwaya GM, von Roenn JH, et al. Randomized phase III trial of liposomal daunorubicin versus doxorubicin, bleomycin, and vincristine in AIDS-related Kaposi's sarcoma. J Clin Oncol 1996 Aug;14(8):2353-64.

ACKNOWLEDGEMENTS

We thank H. Westgeest, resident oncologist and E. Boven, medical oncologist of the VU University Medical Center Amsterdam, for cooperation in the preparation of the manuscripts. We thank R. Otten, clinical librarian of VU University Amsterdam, for his assistance in the literature search. We thank M. den Brok, hospital pharmacist of the VU University Medical Center Amsterdam, for providing pharmacy dispension data. We also thank the medical oncologist and the representative of the HIV patients’ association, for participating in the structured interview.

AUTHOR BIOGRAPHIES

Christel Boons (MSc) is researcher at the Department of Clinical Pharmacology and Pharmacy of the VU University Medical Center Amsterdam, the Netherlands. She is project leader of several oncology trials multicenter performed in the Netherlands focusing on adherence and patients’ experiencing of drug use in daily practice. (no conflict of interest)

Maurits van Tulder (PhD) is professor of Health Technology Assessment at the Department of Health Sciences of the VU University Amsterdam, the Netherlands. He is co-editor of the Cochrane Collaboration Back Review Group (www.cochrane.iwh.on.ca). He is author of more than 230 scientific papers in peer reviewed international journals, of which many report systematic reviews and economic evaluations of diagnostic and therapeutic interventions. His H-index is 39. He is also involved in courses on systematic reviews in Master programs of Health Sciences and Epidemiology at the VU University and at the University of Toronto, Canada. (no conflict of interest)

Cordula Wagner (PhD, physiotherapist en sociologist) works as a professor of patient safety at VU University Medical Center, Amsterdam and is head of the research area 'Quality and Organisation of hospital- and long term care' at NIVEL Netherlands Institute for Health Services Research in Utrecht. Currently she is responsible for the national patient safety research programme in the Netherlands.
For the last 15 years Cordula has been involved in a substantial number of projects focussing on a) the state-of-the-art of the implementation of quality systems among healthcare institutions and professionals, b) the evaluation of quality activities such as guidelines and break through projects, c) the relation between quality systems, care process and clinical outcomes, and d) risk management and patient safety. The research takes place

in various health care fields, e.g. hospital, nursing homes, home health care organisations and mental health care. At the moment Cordula is also participating in a number of European projects focussing on quality and patient safety. (no conflict of interest)

Jacqueline Hugtenburg (PhD, pharmacist, clinical pharmacologist, pharmacologist, epidemiologist) works as an assistant professor at the Department of Clinical Pharmacology and Pharmacy. She is responsible for the pharmacoepidemiological studies of the department. For the last 10 years Jacqueline has been involved in a substantial number of projects focussing a) Pharmacoepidemiology of diabetes mellitus, anxiety and depression and cancer, b) Pharmaceutical care for elderly patients, patients with diabetes and patients with cancer, and c) Studies on drug utilization, drug use in daily practice, and drug safety. (no conflict of interest)

APPENDIX 1

Search strategy.

PUBMED Search History (8-12-2010)

Search	Most Recent Queries	Time	Result
#14	Search #12 AND #9	04:40:14	0
#13	Search #12 AND #7	04:39:51	67
#12	Search #4 AND #11	04:39:24	82
#11	Search paclitaxel[tw] OR taxol[tw]	04:39:06	20510
#10	Search #6 AND #9	04:38:35	12
#9	Search "Costs and Cost Analysis"[Mesh] OR economic*[tw] OR Cost[tiab] OR Costa*[tiab] OR Costb*[tiab] OR Costc*[tiab] OR Costd*[tiab] OR Coste*[tiab] OR Costf*[tiab] OR Costg*[tiab] OR Costh*[tiab] OR Costi*[tiab] OR Costj*[tiab] OR Costk*[tiab] OR Costl*[tiab] OR Costm*[tiab] OR Costn*[tiab] OR Costo*[tiab] OR Costp*[tiab] OR Costq*[tiab] OR Costr*[tiab] OR Costs*[tiab] OR Costt*[tiab] OR Costu*[tiab] OR Costv*[tiab] OR Costw*[tiab] OR Costx*[tiab] OR Costy*[tiab] OR Costz*[tiab]	04:37:55	595806
#8	Search #6 AND #7	04:37:37	242
#7	Search randomized controlled trial [pt] OR controlled clinical trial [pt] OR clinical trial [pt] OR comparative study [pt] OR evaluation studies [pt] OR "randomized controlled trials as topic"[MeSH Terms] OR "random allocation"[MeSH Terms] OR "double-blind method"[MeSH Terms] OR "single-blind method"[MeSH Terms] OR "clinical trials as topic"[MeSH Terms] OR "placebos"[MeSH Terms] OR "research design"[MeSH Terms:noexp] OR "follow-up studies"[MeSH Terms] OR "prospective studies"[MeSH Terms] OR "cross-over studies"[MeSH Terms] OR "drug therapy"[Subheading] OR "clinical trial" [tw] OR "latin square" [tw] OR placebo* [tw] OR random* [tw] OR control[tw] OR controll*[tw] OR prospectiv* [tw] OR volunteer* [tw] OR trial[tiab] OR groups[tiab] OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw]))	04:36:22	6218558
#6	Search #4 AND #5	04:36:07	282
#5	Search doxorubicin*[tw] OR adriamycin*[tw] OR doxil[tw] OR rubex[tw]	04:35:57	44220
#4	Search #1 OR #2 OR #3	04:35:49	12852
#3	Search sarcoma[tiab] AND (hemorrhagic*[tiab] OR haemorrhagic*[tiab])	04:35:30	309
#2	Search Kaposi*[tiab]	04:35:16	10890
#1	Search "Sarcoma, Kaposi"[Mesh]	04:35:02	8368

EMBASE Search History (8-12-2010)

No.	Query	Results	Date
#12	#7 AND #10	8	8 Dec 2010
#11	#10 AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim)	32	8 Dec 2010
#10	#3 AND #9	469	8 Dec 2010
#9	'paclitaxel'/exp OR paclitaxel:mn,tn,ab,ti OR taxol:mn,tn,ab,ti	46270	8 Dec 2010
#8	#5 AND #7	16	8 Dec 2010
#7	'cost benefit analysis'/exp OR 'cost effectiveness analysis'/exp OR 'cost utility analysis'/exp	119589	8 Dec 2010
#6	#5 AND ([cochrane review]/lim OR [controlled clinical trial]/lim	77	8 Dec 2010

No.	Query	Results	Date
	OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim)		
#5	#3 AND #4	1275	8 Dec 2010
#4	'doxorubicin'/exp OR doxorubicin*:mn,tn,ab,ti OR adriamycin*:mn,tn,ab,ti OR doxil:mn,tn,ab,ti OR rubex:mn,tn,ab,ti	111878	8 Dec 2010
#3	#1 OR #2	16559	8 Dec 2010
#2	sarcoma:ab,ti AND (hemorrhagic*:ab,ti OR haemorrhagic*:ab,ti)	302	8 Dec 2010
#1	'kaposi sarcoma'/exp OR kaposi*:ab,ti	16363	8 Dec 2010

Cochrane Search History (25-11-2010)

ID	Search	Hits	Edit	Delete
#1	(kaposi*):ti,ab,kw	168	edit	delete
#2	sarcoma:ab,ti,kw AND (hemorrhagic*:ab,ti,kw OR haemorrhagic*:ab,ti,kw)	2	edit	delete
#3	(#1 OR #2)	169	edit	delete
#4	(doxorubicin* OR adriamycin* OR doxil OR rubex):ti,ab,kw in Clinical Trials	4553	edit	delete
#5	(#3 AND #4)	45	edit	delete
#1	(kaposi*):ti,ab,kw	168	edit	delete
#2	sarcoma:ab,ti,kw AND (hemorrhagic*:ab,ti,kw OR haemorrhagic*:ab,ti,kw)	2	edit	delete
#3	(#1 OR #2)	169	edit	delete
#4	(paclitaxel OR taxol):ti,ab,kw in Clinical Trials	1920	edit	delete
#5	(#3 AND #4)	1	edit	delete