
**Triple therapy of vincristine, bleomycin and etoposide for children with Kaposi sarcoma: Results of a study in Malawian children.**

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Title Page

Triple Therapy of Vincristine, Bleomycin and Etoposide for Children with Kaposi Sarcoma –

Results of a Study in Malawian Children

Marita Macken1, Helen Dale*2, Dominic Moyo3, Eunice Chakmata3, Sarita Depani4, Trijn Israels5,
Dalida Niyrenda3, Simon Bailey6, George Chagaluka3, Elizabeth M Molyneux3

1 Birmingham Children’s Hospital, Steelhouse Lane, Birmingham, B4 6NH, UK.
2 Sheffield Children’s Hospital, Western Bank, Sheffield, S10 2TH, UK.
3 Queen Elizabeth Central Hospital, College of Medicine, Blantyre, Malawi.
4 Great Ormond Street Hospital, London, WC1N 3JH, UK.
5 Princess Maxima Center for Pediatric Oncology, Utrecht, The Netherlands.
6 Sir James Spence Institute of Child Health, Royal Victoria Infirmary, Queen Victoria Road,
Newcastle upon Tyne, NE99 2YB, UK.

Corresponding author: Marita Macken, Department of Paediatric Oncology, Birmingham
Children’s Hospital, Steelhouse Lane, Birmingham, B4 6NH, UK. Tel: 01213339999.
marita.macken@nhs.net.

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<td>Kaposi sarcoma</td>
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<tr>
<td>HIV</td>
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<td>IQR</td>
<td>Interquartile range</td>
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<tr>
<td>CI</td>
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<tr>
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<td>Human herpesvirus 8</td>
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<td>Queen Elizabeth Central Hospital</td>
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<td>VBE</td>
<td>Vincristine, Bleomycin, Etoposide</td>
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Abstract

**Background.** Kaposi sarcoma (KS) is the most common paediatric cancer in HIV-endemic countries of sub-Saharan Africa but there is little research on management and outcomes.

**Methods.** Children with KS at Queen Elizabeth Central Hospital, Blantyre, Malawi treated between August 2012 and March 2015 with six courses of vincristine, bleomycin and etoposide combination chemotherapy including antiretroviral therapy, if HIV-infected, were studied and outcomes compared with previously reported results.

**Findings.** Fifty-six children were included, 38 (68%) were male; 48 (86%) were HIV-positive of whom 36 (77%) were on antiretroviral therapy at diagnosis. Median age at diagnosis was 8 years (IQR 3-12) and median follow-up was 16.9 months (IQR 3.4-36.4). Quality of life improved in 45 (80%) children; the median Lansky Score increased from 80% pre-treatment to 100% post-treatment. Eighteen (32%) children had complete response to treatment. At 12 months overall survival was 71% (95% CI 56-82) and event-free survival (event = death, loss to follow-up or relapse) was 50% (95% CI 36-63). At one-year the risk of loss to follow-up was 13.4%.

In a previous, same-site randomized controlled study of vincristine monotherapy, vincristine and bleomycin or oral etoposide, oral etoposide monotherapy had the best outcome with survival at 12 month of 66% (95% CI 46-80) and event-free survival of 52% (95% CI 33-68); however, loss to follow-up was not reported.

**Conclusion.** Overall survival, event-free survival, and quality of life appear to have improved with this three-agent combination chemotherapy; however larger, randomized studies are needed to determine optimal management.
Introduction

Kaposi sarcoma (KS) is an aggressive, multifocal disease arising from vascular and lymphatic endothelial cells involving the skin and visceral organs. It is the second most frequently diagnosed HIV-related malignancy worldwide and the second most common paediatric tumour in sub-Saharan Africa where HIV and human herpesvirus 8 (HHV-8) are endemic. Neither HIV nor widespread KS is curable and treatment is aimed at disease reduction and improved quality of life.

Antiretroviral therapy (ART) is the first line treatment for AIDS-related KS. ART alone may cause long-term regression of lesions and of localized lymphadenopathy. Systemic chemotherapy is added for patients with extensive skin involvement and disseminated or systemic disease. Adult guidelines recommend first-line usage of liposomal doxorubicin, an expensive drug not readily available in low-income countries. Paediatric data supporting its first line use are not available. Evidence in adults is unclear as to whether alternative regimens are inferior to liposomal doxorubicin.

There are no agreed paediatric KS staging criteria or treatment regimens. The AIDS Clinical Trials Group staging system that classifies tumor (T), immune status (I), and systemic illness (S) was not designed for paediatric KS and does not correlate well with outcomes in this population. There is a new proposed risk stratification system based on clinical characteristics of paediatric KS, and that may identify high-risk patients and guide treatment to improve overall outcomes. Consensus guidelines recommend considering several different treatment regimens. A Cochrane review of four African studies looked at four different chemotherapy regimens: single-agent vincristine, single-agent paclitaxel, bleomycin/vincristine or doxorubicin/bleomycin/vincristine. They concluded that in HIV-infected children ART and chemotherapy together increase the likelihood of KS remission and reduce the risk of death. It is unclear as to which chemotherapeutic regimen is
A study in Zimbabwean adults with KS showed that oral etoposide gave better quality of life with better psychological outcomes, less social disruption and fewer side-effects than supportive care alone, radiotherapy or a 3-drug combination of actinomycin-D, vincristine and bleomycin.\textsuperscript{14} A randomized control trial (RCT) in Malawian children comparing vincristine alone, vincristine with bleomycin and single agent oral etoposide, concluded that survival at one year was better in the oral etoposide and the vincristine/bleomycin groups, compared to vincristine alone. (Survival: deaths for etoposide, $n=21:15$ (66\% [95\% CI 46-80\%]); vincristine/bleomycin, $n=22:12$ (57\% [95\% CI 36-73\%]); vincristine, $n=22:17$ (45\% [95\% CI 26-63\%]); $p=0.045$ at 12 months of follow-up.\textsuperscript{15} During that study clinicians had the impression that etoposide (an anti-angiogenic drug that was given orally) took several weeks to be effective, whereas the vincristine/bleomycin combination worked more quickly. In an attempt to improve survival Malawian children with KS at the Queen Elizabeth Central Hospital (QECH) in Blantyre were treated with a three-drug chemotherapy regimen of vincristine, bleomycin and etoposide (VBE). Thalidomide was given to some children who had treatment failure despite several courses of therapy.

\section*{Methods}

\subsection*{Site}

The QECH is a 1,200 bedded government, tertiary hospital in Blantyre, Malawi. It is the teaching hospital for the medical school and receives referrals for the southern half of the country. The paediatric department admits 28,000 children annually and over 80,000 attend the emergency department and outpatients. The children’s oncology unit has 23 beds and admits 300 patients annually. Children with KS are treated as outpatients unless they are systemically unwell.
Patient data

Data were collected on all children (<16 years) treated for KS with VBE between August 2012 and March 2015. Data included age at presentation, sex, HIV status; location, duration and number of KS cutaneous lesions, lymphadenopathy, oral cavity involvement and presence of pleural effusions, oedema, length of time on ART before the diagnosis of KS, and previous TB treatment. Baseline bloods included haematocrit (PCV), white cell count (WCC), platelets; CD4 cell count and percentage if on ARTs for over a year; weight, sentinel node size and Lansky scores before and after treatment; chemotherapy treatment, response and outcomes.

KS was diagnosed clinically, with biopsy confirmation if the diagnosis was in doubt. Biopsy confirmation was required in 6 cases. HIV infection was confirmed using two rapid tests and eligibility for ART followed national guidelines. Quality of life was assessed using the Lansky score. The chemotherapy regimen consisted of six courses of intravenous vincristine (1.5 mg/m² Day 1), bleomycin (15 IU/m² Day 1) and oral etoposide (100mg/m² Days 1-3). The second course was given after one week and further courses were fortnightly.

Follow up

Children were reviewed one month after completing chemotherapy and six monthly thereafter. Treatment response was assessed by measurement of sentinel KS lesions before and after treatment. Complete response was defined as no clinical evidence of KS; partial response as a decrease of >50% in lesion size; stable disease as <50% reduction and poor response was no response or deterioration in the size of the KS lesions. Relapse was defined as apparent complete recovery followed by a return of the disease. Deaths on treatment were recorded. Patients who did not complete treatment, failed to attend scheduled clinic visits or could not be traced were classified as defaulters after actively attempting to contact them. The time to progression of the disease was noted.
**Data analysis**

Stata version 12.1 (STATA Inc., College Station, TX) was used for analyses. Descriptive analysis included summary statistics of demographic and clinical features. Chi-squared tests were used to calculate p-values for categorical variables and Wilcoxon rank-sum tests for continuous variables. Survival-time and competing risk analyses were used for survival statistics and for Kaplan-Meier plots. Logistic and cox regression were used for univariate and multivariate analysis to calculate hazard ratios and 95% confidence intervals. Multivariate regression analysis was performed in a forwards stepwise fashion including *a priori* variables, or those statistically significant at the 0.10 level in univariate analysis, in the model. We conducted three outcome analyses; 1) Survival: only death was considered as an outcome - defaulters (abandonment) were censored at last follow-up appointment date, 2) Retention: death and default were included together as an event (attrition) 3) Event-free survival: death, default and relapse were combined as an event.

Comparative raw data from the previous randomized controlled study of treatments with vincristine monotherapy or oral etoposide or combined vincristine and bleomycin were re-analysed in the same manner for comparison with our data, and with additional follow-up data compared with that presented in the previous publication.

As this was an audit of departmentally approved standard treatment no formal ethical approval was required.

**Results**
Fifty-six children of whom 38 (68%) were males were enrolled. Median age at diagnosis was 8 years (IQR 3-12). Median weight for age at enrollment was -2.29 (IQR -2.64 - -0.17); but is an unreliable measure of nutrition as many children had tumour related lymphoedema, or missing data (see Table 1). Forty-eight children (86%) had HIV infection of whom 36 (77%) had received ART for a median duration of 10 months (IQR 1.6-23.5). The 12 (23%) ART naïve children commenced ART as soon as possible after diagnosis. The median length of symptoms was 6 months (IQR 1-12) and most children presented with a combination of skin lesions (n=52;93%), lymphadenopathy (n=52;93%) and/or palatal lesions (n=23;41%) (Table 1). The median Lansky score at baseline was 80% (IQR 50-90) and number of treatments given was 6 (IQR 3-6). Seventeen (30.4%) children received additional VBE treatments when they relapsed.

Number of treatments

Not all children survived to receive 6 courses of chemotherapy as many of them had advanced disease. Thirty-four (60.1%) children completed all 6 treatments.

HIV negative children

All eight (14%) HIV-negative children presented with generalized (n=5) or localized (n=3) lymphadenopathy. Six had associated oedema, three had palatal lesions and one had a pleural effusion. Skin lesions if present were few in number. These children were younger (mean age 6.9 (range 2-13 years) than HIV-infected children (mean age 7.9 (range 1-15 years). The ratio of males to females was 7:1 compared to 1:8:1 in HIV-infected children. Two of the 8 children had a sibling who had also been treated for KS. Both were diagnosed by histology and presented with generalized lymphadenopathy. Two children died during treatment, one of the five who completed treatment absconded, three had complete responses, one had a partial response and one had stable disease.

Outcomes
In 18 (32%) children there was complete response to treatment; partial response (>50% reduction in size of sentinel lesion) was seen in 12 (21%), 3 (5%) were stable (<50% reduction) and 7 (12.5%) had no response or disease progression (Table 2).

In 45 (80%) the quality of life, using the Lansky score pre and post treatment, was higher post therapy, 10 (18%) were unchanged and 1 (2%) deteriorated (Table 2).

At 12 months; overall survival was 71% (95% CI 56-82), retention (children remaining after death and default excluded) was 60% (95% CI 45-71) and event-free survival (where event = death, default or relapse) was 50% (95% CI 36-63) (Figures 1a-c). At 24 months follow-up overall survival was 59% (95% CI 44-72) (Table 3).

The risks of death and default were 26·4% (95% CI 16-39) and 13·4% (95% CI 6-24) at 12 months and 36·1% (95% CI 24-49) and 21·1% (95% CI 11-33) at 24 months respectively (Table 4).

Multivariate analysis

Overall, only a greater number of treatments was significantly associated with a protective effect from death, loss to follow up (LTFU) or an event, HR 0·45 (95% CI 0·30-0·69). For children completing treatment previous TB treatment was associated with an increased risk of attrition HR 3·47 (95% CI 0·94-12·75).

Discussion

Studies have shown that a combination of ART and chemotherapy in HIV-KS leads to better outcomes than either treatment alone. Questions still remain as to what is the best chemotherapy
option for disease reduction and for quality of life. Adult studies report that triple drug regimens are better than single or dual drug regimens\(^{21-23}\) Few studies have adequately studied the impact of chemotherapy on KS in children or the most appropriate chemotherapy regimen, especially in resource-limited settings. To our knowledge this is the first report of the use of the combination of vincristine, bleomycin and etoposide (VBE) for children with KS.

Our study shows improvement in survival of children treated for KS with VBE combination therapy at 12 months of 71% (95% CI 56-82) and 24 months 59% (95% CI 44-72), compared to the best performing therapy in the RCT study of individual therapies: oral etoposide with survival of 66% (95% CI 46-80) at 12 months and 43% (95% CI 21-63) at 24 months. However the increased risk of death in the oral etoposide group compared to our VBE combination cohort is not statistically significant on multivariate analysis HR 1.87 (95% CI 0.89-3.94) (Supplementary Table S1). Due to small numbers of children in both of these studies we do not have sufficient power to detect a significant difference at this level.

Our study shows combination VBE therapy has improved complete response rates to treatment; 32% compared to 9% for oral etoposide, 7% for vincristine and 17% for vincristine/bleomycin. As ART therapy significantly affects outcomes in KS, and as there was a significant difference between the duration of ART prior to starting chemotherapy between the VBE cohort and the RCT population, this could be a significant confounder, as shown by loss of significance on multivariate analysis (Supplementary Table S2). However, due to small numbers of children, we did not have the power to detect a significant difference.

There was a higher proportion of children with an improved quality of life post chemotherapy in the VBE cohort (80% v 72% with oral etoposide, the next best performing therapy (Table 2)) but this difference was not statistically significant (Supplementary Table S2).
It is important to consider default as well as death, as loss to follow-up can be missed deaths, and this was not accounted for in previous studies. The risk of default in the RCT was slightly lower at 9.8% (95% CI 2.5-23.1) in the oral etoposide group and 10.7% (95% CI 2.7-25) in the vincristine/bleomycin group at 12 months. This compares to 13.4% (95% CI 5.9-24.1) in our study at 12 months (Table 4). However, overall retention rates (children remaining after excluding death and default) were higher in our study 43% (95% CI 29-55) at 24 months compared to the best performing agent oral etoposide in the RCT 38% (95% CI 18-57) (Table 3).

To separate the effects of chemotherapy from early mortality of very ill children who died of overwhelming disease, the children who completed the full course of treatments were analysed separately. Their survival rates were 87% at 12 months and 75% at 24 months.

Increasing number of treatments was the biggest protective factor for death, attrition and any event (including relapse). This probably reflects that children with more advanced disease or lower CD4 counts at baseline were likely to die early regardless of treatment. Even when the multivariate analysis was repeated without number of treatments, the main protective factor for death and any event was increasing Lansky score at baseline with marginal significance (HR 0.98 and 0.99). Supportive care that includes nutritional support, refund of travel expenses and early management of infection has remained unchanged over the last decade.

In some observational studies HIV-infected children with KS were given various chemotherapies in addition to ART. Of 81 children in Botswana and Malawi, 62 received vincristine/bleomycin and 8 also received doxorubicin. Twenty-three of the 36 (64%) children treated with combination chemotherapy were alive at 12 months. All 14 children treated with single-agent chemotherapy died. Of the children who achieved complete remission, 4 had received vincristine, bleomycin and
doxorubicin and 8 had received vincristine and bleomycin.\textsuperscript{10} A review of 70 children from South African hospitals reported 40\% survival using single or multi-drug combinations of vincristine, doxorubicin and bleomycin in 52 children who were followed for an average of 16 months.\textsuperscript{12} A study of 28 Mozambiquan children treated with paclitaxel and followed for 27 months reported 67\% survival, but 4 children died of drug-related toxicity.\textsuperscript{13} In 73 Ugandan children, 23 of the 24 who received chemotherapy with known outcomes had complete or partial remissions; 17 (70\%) achieved complete remission; 6 achieved partial remission. No difference was observed in outcome when one or two drugs were given. However there was significant loss to follow up, numbers were small and length of follow up was not documented.\textsuperscript{11} It is difficult to compare survival outcomes in all these studies without knowing the stages of the HIV and KS infections and of any co–infections.

All studies, including ours have shown that paediatric KS is more common in males than females and presents at a median age of 8 years. Reassuringly more HIV-infected children in our study were already on ART than in previous studies.

There were fewer earlier deaths when using VBE combination treatment as opposed to single or dual drug treatment. Overall outcome may be similar because of the underlying HIV infection, with non-KS causes of death. Importantly, it is a palliative treatment based on quality of life . Quality of life, essential in the care of KS children, improved with treatment. Children with poor outcomes had the highest increases in Lansky score showing how important a role treatment plays in palliative care. This aspect of care has not been reported in other paediatric KS studies from the African continent.

Limitations
The main limitation to this study, and other paediatric KS studies, were the small numbers. This meant that we could not adequately power our statistical analysis of the various outcomes to detect significant difference in outcomes. Some children were lost to follow-up, although loss 13·4% at 12 months and of 21% at 24 months is comparable to other studies\textsuperscript{11,15} and survival estimates were adjusted for this loss. CD4 counts were incomplete. Risk stratifying patients based on clinical characteristics as proposed by El-Mallawany et al\textsuperscript{8}, may improve overall outcome by guiding treatment more appropriately.

We did not specifically record side-effects of treatment or specifics around cause of death. We were aware of the concerns regarding bleomycin affecting lung interstitium. No clinically significant problems were seen with bleomycin in our patients and though we investigated chest problems as fully as possible it remains difficult to say if signs and symptoms were due to KS, bleomycin or HIV itself. It is also hard to say if some of the HIV-infected children developed KS IRIS after starting ART or it was a new infection. It would be an important consideration for future studies to record toxicity and toxic deaths related to chemotherapeutic agents.

The raw data from the previous RCT study was re-analysed for direct comparison with this study and therefore outcomes vary slightly from those previously reported.

**Conclusion**

This study shows that a combination regimen of vincristine, bleomycin and etoposide for treatment of childhood KS in resource-limited settings may improve survival, response to treatment and quality of life, but numbers were inadequate to confirm significant improvement. Larger clinical trials of this and other chemotherapy options in paediatric populations would validate treatment guidance.
Conflicts of interests

None exist.
Legends

Table 1. Baseline Characteristics of 56 children with Kaposi Sarcoma treated with vincristine, bleomycin and etoposide and 91 children treated in an open randomized study of etoposide v vincristine v bleomycin and etoposide. Statistically significant values (p<0.05) are bolded.

Table 2. Treatment response and change in quality of life of children with Kaposi Sarcoma following treatment with combination therapy; vincristine, bleomycin and etoposide compared with individual therapies.

Table 3. Comparison of survival, retention (children remaining after death & loss to follow-up excluded) and event-free survival (event = death, loss to follow-up or relapse) at 12 and 24 months for VBE combination therapy and individual E, V and VB therapies.

Table 4. Competing risks of death and default at 12 and 24 months for VBE combination therapy and individual E, V and VB therapies.

Supplementary Table S1. Hazard ratios of death, default (loss to follow-up) and event (death, loss to follow-up or relapse) using cox regression for individual drug therapies compared to combination VBE therapy.

Supplementary Table S2. Odds ratios of having poor, stable or partial response to treatment (i.e. not complete response) and odds ratios of deterioration or no improvement in quality of life of study drugs in RCT study compared to VBE combination therapy using logistic regression.

Figures 1A-C. Survival, retention and event-free survival for VBE combination therapy compared to separate E, V, and VB therapies over 24 months.
References


10. Cox CM, El-Mallawany NK, Kabue M et al. Clinical characteristics and outcomes of HIV-


