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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**

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A short running title: Vincristine, Bleomycin, Etoposide in Kaposi Sarcoma

Keywords: Kaposi sarcoma; Vincristine; Bleomycin; Etoposide; Children; Malawi

27

Abbreviation	Full term or phrase
KS	Kaposi sarcoma
HIV	Human immunodeficiency virus
IQR	Interquartile range
CI	Confidence interval
HHV-8	Human herpesvirus 8
ART	Antiretroviral therapy
AIDS	Acquired immune deficiency syndrome
RCT	Randomized control trial
QECH	Queen Elizabeth Central Hospital
VBE	Vincristine, Bleomycin, Etoposide
V	Vincristine
VB	Vincristine, Bleomycin
E	Etoposide
TB	Tuberculosis
LTFU	Loss to follow up
HR	Hazard ratio
CD34	Cluster of differentiation 34
IRIS	Immune reconstitution inflammatory syndrome
WCC	White cell count
PCV	Packed cell volume

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42 **Abstract**

43

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

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

50 **Findings.** Fifty-six children were included, 38 (68%) were male; 48 (86%) were HIV-positive of
51 whom 36 (77%) were on antiretroviral therapy at diagnosis. Median age at diagnosis was 8 years
52 (IQR 3-12) and median follow-up was 16.9 months (IQR 3.4-36.4). Quality of life improved in 45
53 (80%) children; the median Lansky Score increased from 80% pre-treatment to 100% post-
54 treatment. Eighteen (32%) children had complete response to treatment. At 12 months overall
55 survival was 71% (95% CI 56-82) and event-free survival (event = death, loss to follow-up or
56 relapse) was 50% (95% CI 36-63). At one-year the risk of loss to follow-up was 13.4%.

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

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

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67

68 **Introduction**

69

70 Kaposi sarcoma (KS) is an aggressive, multifocal disease arising from vascular and lymphatic
71 endothelial cells involving the skin and visceral organs. It is the second most frequently diagnosed
72 HIV-related malignancy worldwide and the second most common paediatric tumour in sub-Saharan
73 Africa where HIV and human herpesvirus 8 (HHV-8) are endemic.¹ Neither HIV nor widespread
74 KS is curable and treatment is aimed at disease reduction and improved quality of life.

75

76 Antiretroviral therapy (ART) is the first line treatment for AIDS-related KS. ART alone may cause
77 long-term regression of lesions and of localized lymphadenopathy. Systemic chemotherapy is added
78 for patients with extensive skin involvement and disseminated or systemic disease.^{2,3} Adult
79 guidelines recommend first-line usage of liposomal doxorubicin, an expensive drug not readily
80 available in low-income countries.⁴⁻⁶ Paediatric data supporting its first line use are not available.
81 Evidence in adults is unclear as to whether alternative regimens are inferior to liposomal
82 doxorubicin.⁵

83

84 There are no agreed paediatric KS staging criteria or treatment regimens. The AIDS Clinical Trials
85 Group staging system that classifies tumor (T), immune status (I), and systemic illness (S) was not
86 designed for paediatric KS and does not correlate well with outcomes in this population.⁷ There is a
87 new proposed risk stratification system based on clinical characteristics of paediatric KS, and that
88 may identify high-risk patients and guide treatment to improve overall outcomes.⁸ Consensus
89 guidelines recommend considering several different treatment regimens.⁹ A Cochrane review of
90 four African studies¹⁰⁻¹³ looked at four different chemotherapy regimens: single-agent vincristine,
91 single-agent paclitaxel, bleomycin/vincristine or doxorubicin/bleomycin/vincristine. They
92 concluded that in HIV-infected children ART and chemotherapy together increase the likelihood of
93 KS remission and reduce the risk of death. It is unclear as to which chemotherapeutic regimen is

94 most effective.

95 A study in Zimbabwean adults with KS showed that oral etoposide gave better quality of life with
96 better psychological outcomes, less social disruption and fewer side-effects than supportive care
97 alone, radiotherapy or a 3-drug combination of actinomycin-D, vincristine and bleomycin.¹⁴ A
98 randomized control trial (RCT) in Malawian children comparing vincristine alone, vincristine with
99 bleomycin and single agent oral etoposide, concluded that survival at one year was better in the oral
100 etoposide and the vincristine/bleomycin groups, compared to vincristine alone. (Survival:deaths for
101 etoposide, n=21:15 (66% [95% CI 46-80%]); vincristine/bleomycin, n=22:12 (57% [95% CI 36-
102 73%]); vincristine, n=22:17 (45% [95% CI 26-63%]); p=0.045 at 12 months of follow-up.¹⁵ During
103 that study clinicians had the impression that etoposide (an anti-angiogenic drug that was given
104 orally) took several weeks to be effective, whereas the vincristine/bleomycin combination worked
105 more quickly. In an attempt to improve survival Malawian children with KS at the Queen Elizabeth
106 Central Hospital (QECH) in Blantyre were treated with a three-drug chemotherapy regimen of
107 vincristine, bleomycin and etoposide (VBE). Thalidomide was given to some children who had
108 treatment failure despite several courses of therapy.

109

110 **Methods**

111

112 **Site**

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

118

119 **Patient data**

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

127
128 KS was diagnosed clinically, with biopsy confirmation if the diagnosis was in doubt. Biopsy
129 confirmation was required in 6 cases. HIV infection was confirmed using two rapid tests and
130 eligibility for ART followed national guidelines.^{16,17} Quality of life was assessed using the Lansky
131 score.¹⁸ The chemotherapy regimen consisted of six courses of intravenous vincristine (1.5 mg/m²
132 Day 1), bleomycin (15 IU/m² Day 1) and oral etoposide (100mg/m² Days 1-3). The second course
133 was given after one week and further courses were fortnightly.

134

135 **Follow up**

136 Children were reviewed one month after completing chemotherapy and six monthly thereafter.
137 Treatment response was assessed by measurement of sentinel KS lesions before and after treatment.
138 Complete response was defined as no clinical evidence of KS; partial response as a decrease of
139 >50% in lesion size; stable disease as <50% reduction and poor response was no response or
140 deterioration in the size of the KS lesions. Relapse was defined as apparent complete recovery
141 followed by a return of the disease. Deaths on treatment were recorded. Patients who did not
142 complete treatment, failed to attend scheduled clinic visits or could not be traced were classified as
143 defaulters after actively attempting to contact them. The time to progression of the disease was
144 noted.

145

146 **Data analysis**

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

158

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

163

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

166

167

168 **Results**

169

170 Fifty-six children of whom 38 (68%) were males were enrolled. Median age at diagnosis was 8
171 years (IQR 3-12). Median weight for age at enrollment was -2.29 (IQR -2.64 - -0.17); but is an
172 unreliable measure of nutrition as many children had tumour related lymphoedema, or missing data
173 (see Table 1). Forty-eight children (86%) had HIV infection of whom 36 (77%) had received ART
174 for a median duration of 10 months (IQR 1.6-23.5). The 12 (23%) ART naïve children commenced
175 ART as soon as possible after diagnosis. The median length of symptoms was 6 months (IQR 1-12)
176 and most children presented with a combination of skin lesions (n=52;93%), lymphadenopathy
177 (n=52;93%) and/or palatal lesions (n=23;41%) (Table 1). The median Lansky score at baseline was
178 80% (IQR 50-90) and number of treatments given was 6 (IQR 3-6). Seventeen (30.4%) children
179 received additional VBE treatments when they relapsed.

180

181 **Number of treatments**

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

184

185 **HIV negative children**

186 All eight (14%) HIV-negative children presented with generalized (n=5) or localized (n=3)
187 lymphadenopathy. Six had associated oedema, three had palatal lesions and one had a pleural
188 effusion. Skin lesions if present were few in number. These children were younger (mean age 6.9
189 (range 2-13 years) than HIV-infected children (mean age 7.9 (range 1-15 years). The ratio of males
190 to females was 7:1 compared to 1.8:1 in HIV-infected children. Two of the 8 children had a sibling
191 who had also been treated for KS. Both were diagnosed by histology and presented with generalized
192 lymphadenopathy. Two children died during treatment, one of the five who completed treatment
193 absconded, three had complete responses, one had a partial response and one had stable disease.

194

195 **Outcomes**

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

199
200 In 45 (80%) the quality of life, using the Lansky score pre and post treatment, was higher post
201 therapy, 10 (18%) were unchanged and 1 (2%) deteriorated (Table 2).

202
203 At 12 months; overall survival was 71% (95% CI 56-82), retention (children remaining after death
204 and default excluded) was 60% (95% CI 45-71) and event-free survival (where event = death,
205 default or relapse) was 50% (95% CI 36-63) (Figures 1a-c). At 24 months follow-up overall
206 survival was 59% (95% CI 44-72) (Table 3).

207
208 The risks of death and default were 26·4% (95% CI 16-39) and 13·4% (95% CI 6-24) at 12 months
209 and 36·1% (95% CI 24-49) and 21·1% (95% CI 11-33) at 24 months respectively (Table 4).

210

211 **Multivariate analysis**

212 Overall, only a greater number of treatments was significantly associated with a protective effect
213 from death, loss to follow up (LTFU) or an event, HR 0·45 (95% CI 0·30-0·69). For children
214 completing treatment previous TB treatment was associated with an increased risk of attrition HR
215 3·47 (95% CI 0·94-12·75).

216

217

218 **Discussion**

219

220 Studies have shown that a combination of ART and chemotherapy in HIV-KS leads to better
221 outcomes than either treatment alone.^{19,20} 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 regimens²¹⁻²³ 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).

248 .

249 It is important to consider default as well as death, as loss to follow-up can be missed deaths, and
250 this was not accounted for in previous studies. The risk of default in the RCT was slightly lower at
251 9·8% (95% CI 2·5-23·1) in the oral etoposide group and 10·7% (95% CI 2·7-25) in the vincristine/
252 bleomycin group at 12 months. This compares to 13·4 % (95% CI 5·9-24·1) in our study at 12
253 months (Table 4). However, overall retention rates (children remaining after excluding death and
254 default) were higher in our study 43% (95% CI 29-55) at 24 months compared to the best
255 performing agent oral etoposide in the RCT 38% (95% CI 18-57) (Table 3).

256

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

260

261 Increasing number of treatments was the biggest protective factor for death, attrition and any event
262 (including relapse). This probably reflects that children with more advanced disease or lower CD4
263 counts at baseline were likely to die early regardless of treatment. Even when the multivariate
264 analysis was repeated without number of treatments, the main protective factor for death and any
265 event was increasing Lansky score at baseline with marginal significance (HR 0·98 and 0·99).
266 Supportive care that includes nutritional support, refund of travel expenses and early management
267 of infection has remained unchanged over the last decade.

268

269 In some observational studies HIV-infected children with KS were given various chemotherapies in
270 addition to ART. Of 81 children in Botswana and Malawi, 62 received vincristine/bleomycin and 8
271 also received doxorubicin. Twenty-three of the 36 (64%) children treated with combination
272 chemotherapy were alive at 12 months. All 14 children treated with single-agent chemotherapy
273 died. Of the children who achieved complete remission, 4 had received vincristine, bleomycin and

274 doxorubicin and 8 had received vincristine and bleomycin.¹⁰ A review of 70 children from South
275 African hospitals reported 40% survival using single or multi-drug combinations of vincristine,
276 doxorubicin and bleomycin in 52 children who were followed for an average of 16 months.¹² A
277 study of 28 Mozambiquan children treated with paclitaxel and followed for 27 months reported
278 67% survival, but 4 children died of drug-related toxicity.¹³ In 73 Ugandan children, 23 of the 24
279 who received chemotherapy with known outcomes had complete or partial remissions; 17 (70%)
280 achieved complete remission; 6 achieved partial remission. No difference was observed in outcome
281 when one or two drugs were given. However there was significant loss to follow up, numbers were
282 small and length of follow up was not documented.¹¹ It is difficult to compare survival outcomes in
283 all these studies without knowing the stages of the HIV and KS infections and of any co-infections.

284

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

288

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

296

297

298 **Limitations**

299

300 The main limitation to this study, and other paediatric KS studies, were the small numbers. This
301 meant that we could not adequately power our statistical analysis of the various outcomes to detect
302 significant difference in outcomes. Some children were lost to follow-up, although loss 13·4% at 12
303 months and of 21% at 24 months is comparable to other studies^{11,15} and survival estimates were
304 adjusted for this loss. CD4 counts were incomplete. Risk stratifying patients based on clinical
305 characteristics as proposed by El-Mallawany et al⁸, may improve overall outcome by guiding
306 treatment more appropriately.

307

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

315

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

318

319 **Conclusion**

320

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

326

327 **Conflicts of interests**

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329 None exist.

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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.

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