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Kaposi's sarcoma in children: An open randomised trial of vincristine, oral etoposide and a combination of vincristine and bleomycin

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Abstract ***Introduction:*** Kaposi's sarcoma (KS) is a common childhood cancer in places where HIV is endemic and access to antiretroviral therapy (ART) is delayed. Despite this there are no randomised trials to compare and assess chemotherapeutic regimens.
Method: An open label, randomised trial comparing intravenous vincristine alone, vincristine and bleomycin and oral etoposide, was carried out in children with Kaposi's sarcoma in the Queen Elizabeth Central Hospital, Blantyre, Malawi. HIV infected children were given ART after 2–3 courses of chemotherapy if they were not already on treatment. Neither HIV nor widespread KS are curable and treatment is aimed at disease reduction and improved quality of life. Tumour reduction was assessed by measuring the size of sentinel KS nodules and quality of life (QoL) by using the Lansky score. Follow up was until death or for one year.
Findings: 92 children were enrolled of whom 46% were naïve to ART; 10 (11%) were HIV negative. Survival was not influenced by age or gender but was better in the oral etoposide and the vincristine and bleomycin groups. $P = 0.0045$. The group receiving oral etoposide

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had a better quality of life. Toxicity was not significant, and any drop in haemoglobin or white cell count could have been causally related to HIV infection rather than cytotoxic therapy.
Conclusion: Oral etoposide is a safe, effective treatment to contain KS and improve QoL which can be achieved without many visits to the hospital and intravenous injections.

1. Introduction

Before the HIV epidemic, Kaposi's sarcoma (KS) was uncommon, especially in children. In Malawi 11 cases were recorded in the cancer registry between 1967 and 1976 [1]. In the 1980s there was a rapid increase in the number of KS cases in HIV infected people. HIV-related KS affects young people of both sexes and is aggressive, multifocal and widespread involving the skin and visceral organs [2,3]. As the HIV epidemic increased in Africa so did the incidence of KS. It is now one of the most prevalent cancers in all ages in parts of the continent [4–6]. In Malawi it is the most common cancer in adult males (50.7% of total) and the second most common cancer in women and children [7]. Despite being common there are no randomised treatment trials in children and few in adults.

Neither HIV nor widespread KS is curable and treatment is aimed at disease reduction and improved quality of life. Anti-retroviral therapy (ART) is the first line treatment for AIDS-related KS. ART has anti-KS efficacy by inhibition of HIV replication, inhibition in the production of HIV-1 transactivating protein TAT, enhancing immune response against Human Herpes Virus type 8 (HHV8) and possibly through the antiangiogenic activity of protease inhibitors [6,8–10]. In well-resourced settings, with early access to ART, the prevalence of KS has diminished. In low-income settings there is often a delay in the diagnosis of HIV infection and in the starting of ART, and KS remains problematic [11].

In extensive or symptomatic KS, specific treatment of KS in addition to ART is needed. The best therapeutic results in adults have been with liposomal anthracyclines and paclitaxel, but both are expensive and are seldom available in under-resourced countries [12–15]. Other treatments include radiotherapy, laser therapy, immunotherapy, molecular-targeted agents and angiogenesis inhibitors [16,17].

Treatments for children with KS in resource–limited settings are based on adult trials in similar settings. The Malawi national chemotherapy guidelines for KS are to give an intravenous injection of vincristine weekly for 3 weeks and then fortnightly for three further doses [18]. Some independent organisations have combined vincristine and bleomycin in a similar regimen [18]. In Zimbabwe, before ARTs were widely available, a study was undertaken to assess the quality of life and reduction in disease load of adults with KS who received supportive care alone, with radiotherapy, parenteral 3-drug chemotherapy (actinomycin, vincristine and bleomycin) or oral etoposide. Using the Functional Living Index-Cancer (FLI-C), oral etoposide gave better results for hardship, symptoms and physical signs, and was associated with better psychological outcomes, less social disruption and fewer side-effects ($p = 0.004$) [19]. For these reasons we chose to determine the efficacy, tolerability and feasibility of intravenous vincristine versus oral etoposide and versus intravenous vincristine and bleomycin for the treatment of Kaposi's sarcoma in Malawian children.

2. Method

This was an open label, randomised three-arm trial conducted in the Queen Elizabeth Central Hospital (QECH), Blantyre, Malawi. The QECH is a 1200 bedded government referral hospital. The paediatric department admits 28,000 children a year and over 90,000 attend the emergency department and outpatients. The children's oncology unit has 25 beds and admits 340 new cases every year. Children with KS are treated as outpatients unless they are systemically unwell.

Randomisation was computer-generated in blocks of 12. Treatment schedules were in sealed, numbered envelopes and opened sequentially at enrolment. Children were enrolled aged <16 years with clinical evidence of Kaposi's sarcoma. Clinical signs, which in the HIV infected child were often found together, included palatal swellings and discoloration, characteristic purple or brown skin nodules – often with associated brawny oedema, and generalised lymphadenopathy with a negative Mantoux test and no other evidence of tuberculosis (TB), lymphoma or haematological malignancy. Chest signs if present were only concluded to be due to KS if accompanied by bloody, often bilateral, pleural effusions [20]. Diagnosis was confirmed histologically only when there was clinical doubt as to the diagnosis. Guardians gave written consent after being fully informed of the study.

Children who were allergic to study drugs, had received cytotoxic drugs previously, had peripheral neuropathy or were unable to attend for follow-up were excluded from the study.

Many children were already on antiretroviral therapy (ART). Children whose HIV status was unknown were tested after informed consent; if a child was HIV