Aspects of the management of children with cancer in Malawi

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Summary of the PhD thesis

In **chapter 1** we discuss **childhood cancer care in Sub-Saharan Africa.**
We propose a stepwise approach to improve care for children with cancer in balance with and integrated into general paediatric practice. Minimal requirements to do this, feasible interventions and specific challenges are also discussed. Feasible interventions include curative treatment strategies for patients with Burkitt lymphoma and Wilms tumour and adequate symptomatic treatment for patients with Kaposi's sarcoma and others without curative treatment options. Specific challenges include advanced stage of disease at presentation, failure to complete treatment (abandonment), malnutrition and adapting treatment guidelines to the locally available level of supportive care and tolerance of the patients.

In **chapter 2** we describe the **perspectives of the parents** on the disease of their child with cancer and the treatment. This tries to identify factors which could help prevent abandonment of treatment. We found that parents in Malawi are highly motivated to continue with treatment if they think that it will cure their child. None of the interviewed parents had known the diagnosis (cancer) before arrival in the referral hospital. This diagnosis causes fear of recurrence and death. Guardians are reluctant to ask health personnel questions about recurrence and outcome. They worry that taking frequent blood samples will weaken their child. The side effects of the chemotherapy, such as vomiting, are seen as a proof of efficacy.

In **chapter 3** we report the **nutritional status of children with cancer** in Malawi at diagnosis. We found that 55 % (70 of 128) of children with cancer in Malawi are acutely malnourished at admission. Acute malnutrition is defined as an arm muscle area (AMA) below the 5th percentile. Weight for height is not a good assessment of malnutrition in these children as large (often abdominal) masses mask the loss of body weight and detected malnutrition in only 17.2 % (22 of 128) of children in our study. The high rate of acute malnutrition is caused by the high prevalence of undernutrition in Malawian children in general, combined with the often delayed presentation with a malignant disease.

In **chapter 4** the outcome of a **28 day treatment schedule for children with Burkitt lymphoma** in Malawi is reported. Forty consecutive patients, with a mean age of 6.9 years (range 2-15) years, who presented at Queen Elizabeth Central Hospital in Blantyre during 2006, were treated. The initial diagnosis was made on clinical grounds and confirmed on fine needle aspirate in 73%. Chemotherapy in all patients consisted of cyclophosphamide 40mg/kg on day 1, and 60mg/kg on days 8, 18, 28. Intrathecal methotrexate 12.5mg and hydrocortisone 12.5 mg were also administered on days 1, 8, 18, 28. Two patients died during treatment, 3 patients had chemotherapy resistant disease and 35 five patients (88%) achieved a complete

clinical remission by day 28. A relapse occurred in 16 patients after 65-311 (median 137) days. Nineteen patients (48%) are in continued remission for 265-670 (median 454) days. This short inexpensive (drug cost < 50 USD) treatment schedule with limited intensity, cured almost of 50% BL patients in a very resource limited setting.

In **chapter 5** we report the **association** between **malnutrition at diagnosis** and the incidence and outcome of **fever and neutropenia** in patients with **Burkitt lymphoma** during treatment with the local protocol described in the previous chapter. Fifty eight (69 %) of 84 patients with Burkitt lymphoma were acutely malnourished at diagnosis with an arm muscle area (AMA) below the 5th percentile. Malnutrition at diagnosis was associated with a significantly higher rate of profound neutropenia. This association remained significant (OR 12; 95% CI (1.5 - ∞); p=0.012) after control for possible confounders such as clinical stage of disease, bone marrow involvement and HIV infections. All patients with profound neutropenia, prolonged neutropenia and treatment related deaths were malnourished at diagnosis. Four (4.9 %) of 81 patients died of treatment related causes; three of them due to a Gram negative septicaemia. The results of this study show that the intensity of chemotherapeutic regimens has to be adapted to the level of available supportive care and patients' nutritional status and tolerance to avoid unacceptable morbidity and mortality.

In **chapter 6** we report the feasibility, toxicity and efficacy of SIOP **preoperative chemotherapy for Wilms tumour in Malawian children.** Wilms tumour (WT) has a survival rate of 85-90 % in well resourced countries. Social support and counselling were provided to prevent abandonment of treatment. Twenty patients were included, with a mean tumour volume at diagnosis of 2500 ml. Eight patients (40%) presented with metastases. Six of 11 patients (55%) with localized disease and 6 of 8 patients (75%) with metastatic disease had more than 50 % tumour reduction after preoperative chemotherapy. Treatment failure was due to abandonment of treatment (n=2, 10 %), inoperability (n=5, 25 %) and treatment related mortality (n=1, 5%). We concluded that SIOP preoperative chemotherapy for Wilms tumour is feasible, tolerated and efficacious in Malawi. Due to late presentation with advanced stage of disease, resection was not possible in some patients. Early presentation must be encouraged. Despite intense social support abandonment of treatment was still a problem.

In **chapter 7** we report the **nutritional status of patients with Wilms tumour at diagnosis and during treatment.** Serum levels of micronutrients were documented at diagnosis. During therapy oral feeds were encouraged and a locally made ready to use therapeutic peanut butter-based food ('chiponde') supplied.

A high rate of acute malnutrition was found in patients with Wilms tumour at diagnosis (45-55%), much higher than in community controls (11%). Patients (40%) and community controls (37%) had a similar, high rate of stunting (low height for age),which is a sign of chronic malnutrition. Tumour size at diagnosis and the degree of acute malnutrition at diagnosis was correlated; patients with a larger tumour had more severe acute malnutrition ($r=-0.88$, $p<0.01$). With a supply of chiponde, seven of 18 patients had a > 5% increase in corrected weight during preoperative chemotherapy. Patients with a better nutritional course had a better tumour response to chemotherapy ($r=0.52$, $P<0.05$). Surprisingly, few micronutrient deficiencies were found, except for low serum levels of vitamin A (44% of patients). We concluded that acute malnutrition, superimposed on chronic malnutrition, is common in patients with Wilms tumour in Malawi. Earlier presentation needs to be encouraged. Chiponde, a peanut butter based ready-to-use-therapeutic-food, is an attractive means of nutritional support which needs further evaluation.

In **chapter 8** we report the effect of **nutritional status on vincristine pharmacokinetics.** Patients newly diagnosed with Wilms tumour in Malawi and the UK were included. We documented anthropometric parameters, nutritional status and tumour size in newly diagnosed patients with Wilms tumour in Malawi (n=11) and in the UK (n=8). Vincristine plasma concentrations were measured at several time points and vincristine pharmacokinetic parameters (clearance and area under the curve (AUC)) calculated. Malawian patients were more malnourished with a significantly lower mean Z-score of (corrected) weight for height than the UK patients (-2.3 versus 0.42, $p<0.0001$). Vincristine clearance was lower, and exposure to the drug consequently higher in Malawian patients with higher mean logAUC values than in UK patients (3.8 versus 3.5 µg/ml.min, $p=0.003$). The difference in AUC values was statistically significantly explained by nutritional status ($p=0.043$). We conclude that malnourished patients in Malawi exhibit lower vincristine clearance rates and thus higher AUC values than a comparable patient population with a better nutritional status in the UK. In malnourished patients, dose reductions of vincristine may need to be considered to prevent an increased incidence and severity of toxicity.