The Collaborative Wilms Tumour Africa Project; Baseline evaluation of Wilms tumour treatment and outcome in eight institutes in sub-Saharan Africa

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Abstract  
Aim: Reported survival of Wilms tumour in sub-Saharan Africa is below 50%. A published International Society of Pediatric Oncology (SIOP) Pediatric Oncology in Developing Countries (PODC) consensus adapted treatment guideline is implemented as a multi-centre prospective clinical trial at eight centres in sub-Saharan Africa. A baseline evaluation has been done to help decide on priorities to improve outcome and to assess improvements over time.

Methods: A retrospective chart review was performed of patients admitted with Wilms tumour in the three years (2011–2013) preceding the collaborative trial. Patient outcome at the end of treatment was documented for all patients diagnosed in 2011 and 2012. Outcome was classified as (1) alive, no evidence of disease; (2) alive with disease; (3) died during treatment and (4) incomplete treatment. Details on treatment facilities, staff and estimated cost of treatment are documented.

Results: Every year 114–130 patients are diagnosed. The mean survival at end of treatment is 39% (69/176) ranging from 11% to 61%. Incomplete treatment is the most common cause of
treatment failure with 31% (54/176), ranging from 14% to 48% between centres. Twenty-six percent (46/176) of patients died during treatment, ranging from 13% to 37%. Estimated cost of treatment for parents ranged from 100 US$ to 1100 US$ and was considered an important cause of failure to complete treatment.

**Conclusion:** Overall two year survival is estimated at 25%. Prevention of incomplete treatment is possible and will positively affect outcome. Sharing similar local challenges in this regional collaborative project helps to identify and implement feasible, sustainable and successful strategies. © 2014 Elsevier Ltd. All rights reserved.

1. **Introduction**

Wilms tumour is a relatively common childhood renal cancer. Survival of Wilms tumour in high income countries has improved significantly over the last decades and is currently over 85% [1]. Regional collaborative networks, such as the International Society of Pediatric Oncology (SIOP) Renal Tumour Study Group (RTSG) in Europe and the Children’s Oncology Group (COG) in North America have been instrumental in the progress made.

Survival in low-income countries in sub-Saharan Africa is much lower. In many regions treatment is not available. Local challenges to cure include late presentation, limited facilities and trained staff, malnutrition and limited supportive care, all contributing to a higher rate of treatment related mortality [2–4]. The most common cause of treatment failure in low-income countries is incomplete treatment that is sometimes called abandonment of treatment [5]. The reasons for this are many, all of them related to poverty and perception of cancer incurability [6].

Reported Wilms tumour survival rates in sub-Saharan Africa are from 11% in Sudan with a high rate of treatment abandonment to 46% in Malawi [7]. In Blantyre, Malawi, an adapted treatment guideline with preoperative chemotherapy, nutritional support and social support to enable parents to complete treatment for their child was implemented in 2008. This improved projected survival from below 30% to 46% [8,9].

The Paediatric Oncology in Developing Countries (PODC) section of the International Society of Paediatric Oncology (SIOP) produced consensus guidelines for the management of children with Wilms tumour and supportive care in ‘setting 1’. This is defined as a setting where only the minimal requirements for treatment with curative intent are available [10,11]. These minimal requirements for Wilms tumour treatment include basic laboratory and radiology facilities, adequate surgical facilities and a trained surgeon; chemotherapy and facilities for its safe administration and supportive care [10].

The treatment guideline is based on the SIOP Wilms Tumour 2001 protocol and includes preoperative chemotherapy with a reduced dosage of doxorubicin, optional prolongation of preoperative chemotherapy for large, localised tumours and a simplified postoperative chemotherapy stratification which allows for the absence of radiotherapy [10].

The Collaborative Wilms Tumour Africa Project (http://paedonc.wix.com/wilmsafrica) is a collaboration of eight centres in five countries in sub-Saharan Africa. These centres are in Ethiopia (Addis Ababa), Ghana (Accra and Kumasi), Cameroon (Mbingo, Mutengene, Banso), Malawi (Blantyre) and Uganda (Kampala). In all these centres the minimal requirements for treatment with curative intent of children with Wilms tumour have been available for some years. The project (clinical trial registration number NCT01991652) will implement the SIOP PODC consensus treatment guideline as a multi-centre prospective clinical trial with uniform outcome evaluation [12,13]. Enrolment of patients started in January 2014 following local IRB (Institute Research Board) approval.

In this paper we describe the baseline situation in the participating centres with reference to the available facilities, treatment and outcome of children with a Wilms tumour in the three years (2011–2013) preceding the collaboration.

2. **Methods**

A retrospective analysis was done of the end of treatment outcome as this information was expected to be available in the treatment files of all patients at all collaborating centres.

The collaborating centres are in Kumasi, Ghana (Komfo Anokye Teaching Hospital); Accra, Ghana (Korle Bu Teaching Hospital); Kampala, Uganda (Uganda Cancer Institute); Blantyre, Malawi (Queen Elizabeth Central Hospital); Cameroon (Mbingo, Mutengene and Banso Baptist Hospitals) and Addis Ababa (Tikur Anbessa Specialized Hospital).

The centres in Ghana, Uganda, Malawi and Cameroon had a patient registration system for all newly diagnosed children with cancer and all patients with Wilms tumour were included. In Ethiopia, there was no patient registration system and the figures have been collected by retrospectively going through in-patient ward registry books.
Follow up of patients is a major challenge in sub-Saharan Africa. Many patients do not return for follow up visits (no money for travel, other competing priorities) and active follow up is both expensive and difficult when home addresses are not available and roads are in a bad condition [13].

Outcome at the end of treatment was evaluated for the patients diagnosed in 2011 and 2012. For patients diagnosed in 2013 this was not evaluated as many of them were still on treatment when the analysis was performed. Outcome at end of treatment was divided into four categories; alive and no evidence of disease, alive with remaining disease, not alive (died during treatment) and incomplete treatment.

Further information was collected through semi-structured interviews with the medical representatives of the institutes. This included the type of hospital, the history of treating children with cancer, clinical facilities, personnel, twinning partnerships and funding support. We also documented the estimated average cost of treatment for parents. Factual information about the country’s health and economic status was found in the UNICEF ‘State of the world’s children’ 2014 report.

In all centres minimal requirements for treatment of children with Wilms tumour with curative intent are available as this is a prerequisite to join the collaboration. These minimal requirements are defined and described in the SIOP PODC consensus treatment recommendations [10].

3. Results

The participating centres are situated in different regions in sub-Saharan Africa (Fig. 1). All are low-income countries. Table 1 shows some demographic, socio-economic and health characteristics of the countries [14]. The gross national income per capita is commonly used as a parameter of wealth of a country and has been shown to correlate with postulated 5 year childhood cancer survival in low income countries [15].

Most hospitals are large, government, university teaching hospitals. The three hospitals in Cameroon are smaller Baptist hospitals in a rural area. Table 2 shows some general features of the participating centres. All centres have some external funding support and a partnership with centres in high-income countries. The centres in Malawi, Ghana and Cameroon have twinning partnerships which are supported through a World Child Cancer grant. All centres have dedicated, experienced nurses, though none have formal paediatric

Fig. 1. Map showing the location of the participating centres.
oncology training. Most nurses have received some training through twinning workshops.

Table 3, shows the number of new patients with Wilms tumour that were diagnosed in the participating treatment centres in 2011–2013.

In Ethiopia, as shown in Table 3, 120 patients were registered with a diagnosis of Wilms tumour in the inpatient ward registry books between 2011 and 2013 but only 32 files could be retrieved. We did not include the results of the evaluation of outcome at end of treatment of these 32 children in Table 4 and in the overall analysis, because of a potentially significant selection bias. Of these 32 patients, two were misdiagnosed. The end of treatment evaluation of the remaining 30 (100%) patients showed: 11 (37%) alive, no evidence of disease; no (0%) patients alive with disease, five (17%) died during treatment and 14 (47%) did not complete their treatment.

Table 4 shows the end of treatment outcome of all Wilms tumour patients diagnosed in 2011 and 2012 in the other centres in Ghana, Uganda, Malawi and Cameroon. In these centres respectively 22 (Kumasi), 24 (Accra), 54 (Kampala), 59 (Blantyre) and 17 (Cameroon) Wilms tumour patients were diagnosed in the years 2011 and 2012 combined. Files of all these children were available and they are all included in the evaluation of outcome.

Table 5 shows some information about the estimated cost of treatment and which costs are covered by the government, by health insurance (if available) and by

Table 1
Demographic, Health and Socio-economic indicators countries [14].

<table>
<thead>
<tr>
<th></th>
<th>Ghana</th>
<th>Uganda</th>
<th>Malawi</th>
<th>Cameroon</th>
<th>Ethiopia</th>
</tr>
</thead>
<tbody>
<tr>
<td>GNI(^a) per capita (US$)</td>
<td>1550</td>
<td>440</td>
<td>320</td>
<td>880</td>
<td>380</td>
</tr>
<tr>
<td>Under 5 mortality rate (1990)</td>
<td>128</td>
<td>178</td>
<td>244</td>
<td>135</td>
<td>204</td>
</tr>
<tr>
<td>Under 5 mortality rate (2012)</td>
<td>72</td>
<td>69</td>
<td>71</td>
<td>95</td>
<td>68</td>
</tr>
<tr>
<td>Population &lt;5 years ( ( \times 10^6 ) ) (2012)</td>
<td>3.6</td>
<td>6.9</td>
<td>2.9</td>
<td>3.6</td>
<td>14.1</td>
</tr>
</tbody>
</table>

\(^a\) GNI – gross national income.

Table 2
General features participating centres.

<table>
<thead>
<tr>
<th></th>
<th>KATH(^a)</th>
<th>KBTH(^b)</th>
<th>UCT(^c)</th>
<th>QECH(^d)</th>
<th>MM&amp;B(^e)</th>
<th>TASH(^f)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New childhood cancer patients per year</td>
<td>100</td>
<td>150</td>
<td>450</td>
<td>200</td>
<td>125</td>
<td>500–600</td>
</tr>
<tr>
<td>Inpatient beds for children with cancer</td>
<td>12</td>
<td>15</td>
<td>23</td>
<td>24</td>
<td>16</td>
<td>40</td>
</tr>
<tr>
<td>Childhood cancer treatment since</td>
<td>1998</td>
<td>1968</td>
<td>1967</td>
<td>&gt;40 years</td>
<td>2004</td>
<td>&gt;40 years</td>
</tr>
<tr>
<td>Night</td>
<td>1:20</td>
<td>1:12</td>
<td>1:40</td>
<td>1:30</td>
<td>1:10</td>
<td>1:10</td>
</tr>
<tr>
<td>Paediatricians’ training</td>
<td>Trained paediatric oncologist</td>
<td>Trained paediatric oncologists</td>
<td>Trained paediatric oncologist</td>
<td>Experienced paediatric oncologist</td>
<td>Experienced clinicians</td>
<td>Trained paediatric oncologist and fellows</td>
</tr>
<tr>
<td>Surgeons’ training</td>
<td>Paediatric surgeon</td>
<td>Paediatric surgeon</td>
<td>Paediatric surgeon</td>
<td>Paediatric surgeon</td>
<td>Experienced surgeon</td>
<td>Paediatric surgeon</td>
</tr>
<tr>
<td>Patient registration</td>
<td>Excel</td>
<td>POND</td>
<td>Excel</td>
<td>Excel</td>
<td>POND</td>
<td>Hard copy Registry logbook</td>
</tr>
<tr>
<td>Wilms tumour treatment protocol before 2014</td>
<td>SIOP 2001</td>
<td>SIOP 2001</td>
<td>NWTG(^g)/SIOP 2001(^h)</td>
<td>SIOP PODC</td>
<td>Modified SIOP 2001</td>
<td>SIOP PODC</td>
</tr>
<tr>
<td>Radiotherapy (Cobalt machine)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Pathology</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Results in time to stratify postoperative chemotherapy</td>
<td>Sometimes too late</td>
<td>Sometimes too late</td>
<td>Sometimes too late</td>
<td>Often too late</td>
<td>Sometimes too late</td>
<td>Often too late</td>
</tr>
</tbody>
</table>

\(^a\) Komfo Anokye Teaching Hospital, Kumasi, Ghana.
\(^b\) Korle Bu Teaching Hospital, Accra, Ghana.
\(^c\) Uganda Cancer Institute, Kampala, Uganda.
\(^d\) Queen Elizabeth Central Hospital, Blantyre, Malawi.
\(^e\) Mbingo, Mutengene & Banso Baptist Hospitals, Cameroon.
\(^f\) Tikur Anbessa Specialized Hospital; Addis Ababa, Ethiopia.
\(^g\) NWTG = National Wilms Tumour Study Group.
\(^h\) SIOP = International Society of Paediatric Oncology; PODC = Paediatric Oncology in Developing Countries.
the oncology programme with external support (if available). We estimated the remaining average costs for the parents.

4. Discussion

The aim of this audit is to evaluate and document the ‘baseline’ situation of Wilms tumour treatment and outcome in the centres participating in the SIOP Africa/PODC collaborative Wilms tumour project. This will help to decide what our priorities should be in order to improve outcome and will help in assessing improvements over time.

The results of the evaluation of outcome are sobering. Average end of treatment survival is 39% (69/176) and ranges from 11% in Kampala to 61% in Blantyre. This only reflects short-term results. Overall survival will be lower as some children will have a relapse of disease with longer follow up. A previous analysis in Blantyre (2009–2010) showed that 15% of children had a relapse after treatment, with 46% projected survival after a median follow up of 18 months [8]. These figures correspond well with the current results for Malawi and provide an estimate of average overall two year survival of approximately 25% in this baseline evaluation.

The evaluation also provides insight into the causes of death; incomplete treatment, death during treatment (considered toxicity) and treatment related deaths. Each cause needs a different response to be able to improve outcome. For example; earlier diagnosis and more intense treatment (e.g. include radiotherapy) would reduce disease related deaths; improved supportive care and reduced intensity treatment would reduce toxic deaths; and good counselling and free medical treatment including social support (e.g. money for travel) would reduce the rate of incomplete treatment.

In the whole group, 31% (54/176) of patients did not complete treatment, the rates of this ‘abandonment’ of treatment ranging from 14% to 48%. This is largely preventable and it is the most common cause of treatment failure/death in low-income countries [5,7]. Poverty, direct cost of treatment and associated costs for the family play a major role [16]. All centres have been trying to prevent abandonment of treatment, but funds are not sufficient to provide parents with financial support to cover all their costs. Estimated remaining costs for parents range from around 100 US$ in Malawi to around 1100 US$ in Ghana. Poor parents simply cannot afford this and have to stop the treatment.

With sufficient funds incomplete treatment is a largely preventable cause of treatment failure. A few years ago external funds paid for all treatment and associated costs (food, transport) for children with Wilms tumour in Malawi. This, combined with careful counselling on the need to complete treatment and a professional and caring atmosphere on the ward brought the rate of incomplete treatment down to 6%. The majority of these 6% were children of Jehovah’s Witnesses who refused a
<table>
<thead>
<tr>
<th>Health insurance</th>
<th>Kath^{a}</th>
<th>KBTH^{b}</th>
<th>UCI^{c}</th>
<th>QECH^{d}</th>
<th>MM&amp;B^{e}</th>
<th>TASH^{f}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health insurance covers</td>
<td>Hospital stay, basic lab investigations, supportive care drugs, part of surgery costs</td>
<td>n.a.</td>
<td>n.a.</td>
<td>Chemotherapy</td>
<td>Chemotherapy</td>
<td>n.a.</td>
</tr>
<tr>
<td>External/twinning support oncology program covers</td>
<td>Some chemotherapy</td>
<td>Some chemotherapy</td>
<td>None</td>
<td>Chemotherapy</td>
<td>Food</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Government/Mission Hospital covers</td>
<td>X-ray, Ultrasonography</td>
<td>Chemo 500</td>
<td>Surgery 350</td>
<td>Food</td>
<td>Food 30</td>
<td>Surgery 300</td>
</tr>
<tr>
<td>Treatment costs for the patients (in US$)</td>
<td>X-ray/USS 50</td>
<td>Chemo 500</td>
<td>Surgery 350</td>
<td>Surgery 300</td>
<td>Surgery 300</td>
<td>Surgery 300</td>
</tr>
<tr>
<td>Money for travel All/some/none covered</td>
<td>Not covered</td>
<td>Not covered</td>
<td>Not covered</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
</tr>
<tr>
<td>Board and lodging Free/none covered</td>
<td>Not covered</td>
<td>Mother’s hostel (free)</td>
<td>21 beds free when available else sleep on floor and on veranda</td>
<td>Free</td>
<td>Not covered</td>
<td>30 beds, free when available</td>
</tr>
<tr>
<td>Food during stay in the hospital</td>
<td>Provided, sufficient</td>
<td>Provided, not sufficient</td>
<td>Some hospital food – not enough</td>
<td>Some</td>
<td>Yes</td>
<td>Some hospital food – not enough</td>
</tr>
<tr>
<td>Active counselling No/yes: doctor, nurse, social worker</td>
<td>Yes D + N</td>
<td>Yes D + N</td>
<td>1 counsellor for the whole ward (adults and children): not enough</td>
<td>Yes by palliative care team who have a wide counselling remit</td>
<td>Yes D + N SW</td>
<td>Not really, no counsellor, only clinical information</td>
</tr>
<tr>
<td>Follow up system</td>
<td>No</td>
<td>Phone calls</td>
<td>No</td>
<td>Phone calls and active follow up</td>
<td>Active follow up</td>
<td>No</td>
</tr>
</tbody>
</table>

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a Komfo Anokye Teaching Hospital, Kumasi, Ghana.
b Korle Bu Teaching Hospital, Accra, Ghana.
c Uganda Cancer Institute, Kampala, Uganda.
d Queen Elizabeth Central Hospital, Blantyre, Malawi.
e Mbingo, Mutengene & Bango Baptist Hospitals, Cameroon.
f Tikur Anbessa Specialized Hospital; Addis Ababa, Ethiopia.
blood transfusion around surgery and so could not be operated with safety.

For our collaborative project successful strategies to prevent incomplete treatment will have the largest positive impact on survival. The comprehensive treatment protocol includes a chapter on these strategies, including the need for careful documentation of contact phone numbers, how to get to patients homes and the need for adequate counselling and financial support if needed and available. The project has some funding to cover patients’ costs, but not enough to cover them all. It also needs to be recognised that it is ethically difficult to cover all costs for one patient group (e.g. Wilms tumour) and not for others if they stay for weeks on the same ward. The aim is to reduce the average rate of incomplete treatment in the collaborative project to below 10%.

Twenty-six percent (46/176) of patients died during treatment, ranging from 13% to 37%. When children die during treatment it is difficult to distinguish between a disease related and a treatment related cause. In our centres children often present late with severe malnutrition and advanced disease. To be sure to avoid treatment related deaths we assume all children who die during treatment are due to the treatment. In the adapted treatment guideline the dosage of doxorubicin is reduced to 35 mg/m², from 50 mg/m² in the (European) SIOP Wilms Tumour 2001 protocol [17]. In Malawian malnourished patients the standard SIOP preoperative chemotherapy caused significant haematological toxicity [18]. Apart from a reduced intensity treatment protocol; adequate, locally optimal supportive care is needed to prevent treatment related deaths. Nursing care is crucial [19]. Fortunately all units have dedicated, experienced nurses, though the patient to nurse ratio (up to 1:10 in the day; 1:40 in the night) is challenging. The comprehensive protocol includes a detailed section on adapted supportive care, based on the SIOP PODC guideline which includes recommendations on nutritional support, pain management and locally feasible and adequate management of febrile neutropenia [11]. The aim is to reduce the average rate of treatment related deaths in the collaborative project to below 10%.

As discussed previously the percentage of children with disease related deaths cannot be judged from this evaluation of outcome at the end of treatment as there is no long term follow up.

Adequate patient registration and record keeping is crucial to do the analyses as presented in this paper and has been available in most of the participating centres which have been well established childhood cancer treatment centres for several years, for Ethiopia it has now been set up. For the more detailed data collection in the prospective clinical study a concise and specific case record form has been developed. For longer term follow up patient details and follow up status are entered into excel.

In describing the centres’ facilities we have focused on the training level of the staff and on some general features of both the centre and the country. Most of these are to enable us to understand the treating environment and contextualise Wilms tumour management. Collaborating centres all have minimal requirements for treating children with Wilms tumour as this is a prerequisite to join the collaboration. Most participating centres heard about this project at international childhood cancer (SIOP) meetings and other centres may not have been represented at those meetings. These centres may not reflect the overall care of children with cancer in sub-Saharan Africa.

In conclusion, overall long term survival is estimated at 25%. Incomplete treatment is the most common cause of treatment failure and successful strategies to prevent this will have the largest positive impact on survival. Adequate financial support is needed for this and it is a priority. We aim to use funds effectively in the local context. Reduced intensity treatment and adequate supportive care will hopefully reduce treatment related deaths. Sharing similar local challenges in this regional collaborative project helps to identify and implement feasible, sustainable and successful strategies.

Authors contribution

V.P., H.D., J.K., L.R., F.K., P.H., T.I. and E.M. collected the data. TI and EM drafted the paper. All authors revised, commented and edited the paper.

Conflict of interest statement

None declared.

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References


