Improvement of overall survival in the Collaborative Wilms Tumour Africa Project

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Abstract

Introduction: The Collaborative Wilms Tumour (WT) Africa Project implemented an adapted WT treatment guideline in six centres in sub-Saharan Africa. The primary objectives were to describe abandonment of treatment, death during treatment, event-free survival (EFS) and relapse following implementation. An exploratory objective was to compare outcomes with the baseline evaluation, a historical cohort preceding implementation.

Methods: The Collaborative WT Africa Project is a multi-centre prospective clinical trial that began in 2014. Funding was distributed to all participating centres and used to cover treatment, travel and other associated costs for patients. Patient characteristics, tumour characteristics and events were described.

Results: In total, 201 WT patients were included. Two-year EFS was 49.9 ± 3.8% when abandonment of treatment was considered an event. Relapse of disease occurred in 21% (42 of 201) of all included patients and in 26% (42 of 161) of those who had a nephrectomy. Programme implementation was associated with significantly higher survival without evidence of disease at the end of treatment (52% vs 68.5%, \( P = 0.002 \)), significantly reduced abandonment of treatment (23% vs 12%, \( P = 0.009 \)) and fewer deaths during treatment (21% vs 13%, \( P = 0.06 \)).

Conclusion: This collaborative implementation of an adapted WT treatment guideline, using relatively simple and low-cost interventions, was feasible. Two-year EFS was almost 50%. In addition, a significant decrease in treatment abandonment and an increase in survival at the end of treatment were observed compared to a pre-implementation cohort. Future work should focus on decreasing deaths during treatment and will include enhancing supportive care.

KEYWORDS  
abandonment, paediatric oncology, SIOP PODC, supportive care, survival, Wilms tumour

1 INTRODUCTION

Wilms tumour (WT) is a childhood kidney tumour. It is one of the common and curable cancer types targeted by the Global Initiative for Childhood Cancer, launched by the World Health Organization (WHO), with a goal to improve outcomes globally.1,2 Multi-centre clinical trials in high-income countries using a combination of chemotherapy, surgery and radiotherapy have resulted in remarkable improvement in overall survival rates to above 85%.3 However, outcomes are substantially worse in low-income countries. Estimated survival in most African countries is much lower, with a documented 5-year overall survival of 42% in Malawi and 11% survival with short follow up in

Abbreviations: EFS, event-free survival; PODC, pediatric oncology in developing countries; SIOP, International Society of Pediatric Oncology; SUCCOUR, Supportive Care for Children with Cancer in Africa; WHO, World Health Organization; WT, Wilms tumour.
Sudan.4,5 These poorer outcomes have been attributed to many factors including late presentation with advanced disease, inability to afford therapy, nonavailability of drugs and difficult access to essential services including adequate supportive care.

The Collaborative WT Africa Project started in 2014. The aim was to share data and local experiences using the consensus treatment guideline of the International Society of Pediatric Oncology pediatric oncology in developing countries (SIOP PODC) as the standard of care.6,7

Primary objective was to describe abandonment of treatment, death during treatment, event-free survival (EFS) and relapse following implementation of the Collaborative WT Africa Project. Exploratory objective was to compare outcomes between the adapted WT cohort and a historical cohort preceding implementation.

### 2 | METHODS

This prospective multi-centre clinical trial included implementation of the treatment guideline, adapted to local circumstances, and uniform patient registration and evaluation of outcome in all participating centres. Funding was distributed to all participating centres and used to partially cover treatment, travel and other associated costs for patients.

#### TABLE 1  Patient and tumour characteristics at diagnosis (n = 201)

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age in years (range)</td>
<td>3.6 (0.3-13.4)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>118 (59%)</td>
</tr>
<tr>
<td>Duration of symptoms &gt; 2 months, n (%)</td>
<td>103 (51%)</td>
</tr>
<tr>
<td>History of weight loss, n (%)</td>
<td>159 (79%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumour characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour side</td>
<td></td>
</tr>
<tr>
<td>Tumour left side</td>
<td>108 (54%)</td>
</tr>
<tr>
<td>Tumour right side</td>
<td>93 (46%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Localised or metastatic</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Localised</td>
<td>139 (69%)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>62 (31%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site metastases</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>48</td>
</tr>
<tr>
<td>Liver</td>
<td>13</td>
</tr>
<tr>
<td>Lung and liver</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median tumour size in cm (range)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>By tape measure (n = 152)</td>
<td>17 (2-40)</td>
</tr>
<tr>
<td>By imaging (n = 133)</td>
<td>14 (2-29)</td>
</tr>
</tbody>
</table>

*Patients may have multiple sites of metastasis.

*Brain metastasis, peritoneum, not specified.

Patient enrolment began in January 2014, after local Institutional Research Board (IRB) approval was obtained at each centre. Patients were included prospectively from January 2014 in six centres in Malawi (Blantyre), Cameroon (Mbingo, Banso, Mutengene) and Ghana (Accra and Kumasi). All these centres had curative intent treatments for WT available.6 Only the centres in Ghana (Accra and Kumasi) had access to radiotherapy for their patients. This protocol was registered (NCT01991652). Patient inclusion for this report was completed in January 2018, after a 4-year period.

All patients with a clinical and ultrasound diagnosis of a unilateral WT were included. Those with histological findings incompatible with WT were excluded as were those with bilateral WT. A detailed description of the adapted WT treatment guideline is reported elsewhere.6,8 All patients had plain chest radiography and ultrasound of the abdomen to document tumour size and the presence of metastases. Pre-operative chemotherapy consisted of a 4-week two-drug or 6-week three-drug regimen depending on the presence of local or metastatic disease, respectively, with optional treatment prolongation in the case of large tumours. Patients weighing less than 12 kg or with severe acute malnutrition had a one-third dose reduction of all chemotherapy. Post-operative chemotherapy was stratified by pathological stage and risk classification of the tumour, if available, or by surgical stage.6 Postoperative chemotherapy was according to the SIOP PODC guidelines for centres in Malawi and Cameroon. In Ghana, where radiotherapy was available, postoperative chemotherapy was
Patient details (age and sex), duration of history and observed weight loss were documented. Tumour size was determined both clinically by means of a tape measure and by imaging (ultrasound or computerised tomography scan).

Outcome at the end of treatment was categorised as (a) alive without evidence of disease, (b) treatment abandonment, (c) death during treatment, (d) persistent disease (unresectable disease, relapse of disease, or persistent disease after the completion of the full treatment), or (e) death from other cause. Survival time was calculated from diagnosis to the last moment of contact, either by clinic visit or active follow up (phone or in person).

In order to conduct exploratory comparative analysis, we retrospectively collected data on treatment outcomes for those who would have met eligibility criteria for this multi-centre study but presented in the 2 years prior to programme implementation. Only treatment outcome could be abstracted and not demographic details or other outcomes due to resource constraints. These outcomes have been reported previously.8,9 Statistical analysis was performed using SPSS 22.0. Survival was calculated using a Kaplan-Meier curve. A Pearson chi-square test, test of independence, was used to compare the end-of-treatment outcome between the two cohorts. A P-value < .05 was considered statistically significant.

**3 | RESULTS**

From January 2014 to January 2018, 201 patients were enrolled prospectively as follows: 75 from Blantyre (Malawi), 69 from Accra (Ghana), 37 from Mbongo, Banso and Mutengene (Cameroon) and 20 from Kumasi (Ghana). Figure 1 shows the flow diagram of patient identification, enrolment and completion of treatment.

Table 1 shows the patient and tumour characteristics of enrolled participants. Tumours of 38% (50/133) of patients had a maximum diameter greater than 15 cm on imaging. Metastases were detected at diagnosis in 31% (62/201) of patients.

Two-year EFS (Figure 2) was 49.9% with a median follow up of 27 months (range 1-58 months) with abandonment of treatment considered an event.

Table 2 shows the outcome of patients at the end of treatment in the prospective multi-centre study.

Of the 201 patients, 24 (12%) abandoned treatment, 27 (13%) died during treatment and 47 (23%) had a disease-related cause of treatment failure either before or after the end of planned treatment. Two patients died of another cause. Of the 201 patients, 42 (21%) had a relapse of disease after a median follow up of 27 months (range 1-58 months) with abandonment of treatment considered an event.

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TABLE 2  End-of-treatment outcome comparison between the 2014-2018 cohort and the 2011-2012 cohort (baseline evaluation)

| End-of-treatment outcome                  | 2011-2012 n = 122 | 2014-2017 n = 201 | P-value*
|------------------------------------------|-------------------|------------------|----------
| Alive, no evidence of disease            | 63 (52%)          | 138 (68.5%)      | .002     
| Abandonment of treatment                 | 28 (23%)          | 24 (12%)         | .009     
| Death during treatment                   | 26 (21%)          | 27 (13%)         | .064     
| Disease-related event                    | 5 (4%)            | 11 (5%)          | .81      
| Death other cause                        | 0                 | 1 (0.5%)         | N.S.     
| Total                                    | 122 (100%)        | 201 (100%)       |          

*Death before start of therapy, persistent disease, relapse.

and 28% (31/112) in centres without radiotherapy and a shorter postoperative chemotherapy (in Cameroon and Malawi; P = .008).

Of the 201 patients, 161 had a nephrectomy. In this group of patients who had a nephrectomy, 42 of 161 (26.1%) had a relapse. If we exclude the one patient who was <6 months old, then 42 of 160 (26.2%) had a relapse of disease.

Table 2 also compares the outcomes at the end of treatment between the pre-implementation and the post-implementation cohort. Programme implementation was associated with significantly higher survival without evidence of disease at the end of treatment (52% vs 68.5%, P = .002), reduced abandonment of treatment (23% vs 12%, P = .009) and less death during treatment (21% vs 13%, P = .06).

4 | DISCUSSION

This paper reports on one of the few multi-centre clinical trials for childhood cancer in Africa. It demonstrates the benefits of a regional collaborative network. This network identifies shared local challenges and develops and implements sustainable interventions, giving priority to those with the highest expected impact on survival. Implementation and evaluation of an adapted treatment guideline was feasible.

Compared to the baseline evaluation of the pre-implementation cohort, the programme was associated with significantly higher survival without evidence of disease at the end of treatment, reduced abandonment of treatment and reduced death during treatment.

Although we achieved 2-year EFS of 49.9 ± 3.8%, this is still much lower than survival in high-income countries.

Reliable childhood cancer survival data are rare in sub-Saharan Africa. Follow up of patients to establish these data is extremely challenging, given the other priorities of parents than to come for review with a healthy child, limited resources, bad roads and lack of addresses for clinic staff to be able to follow up. Consequently, the follow up of the pre-implementation cohort is limited. Analysis of end-of-treatment outcome, without longer-term follow up, is useful though and gives relevant information as it will determine the number of patients who died during treatment and abandoned treatment.

The frequency distribution of causes of treatment failure in low-income countries differs from those in high-income settings. These causes include abandonment of treatment, death during treatment and disease-related causes such as unresectable disease or relapse of disease. Each of these causes requires specific interventions to improve results as described below. Abandonment of treatment was reduced from 23 to 12%. Our objective is to decrease it further. It is often the most common cause of treatment failure in low-income countries and shown to be largely preventable with financial support for medical treatment and associated costs, adequate counselling and other appropriate interventions. In our opinion, the funding support to partially cover treatment, travel and other associated costs for patients played an essential role in the reduction of abandonment of treatment in our programme.

Similarly, the number of patients who died during treatment decreased from 21 to 13%. It was not possible to distinguish between treatment-related mortality or progressive disease in these patients. Death during treatment is assumed to be related to acute malnutrition, late presentation with severe disease and limited supportive care, especially nursing capacity. Interventions to reduce deaths during treatment could include either decreasing intensity of treatment or to improve supportive care. Decreasing intensity of treatment in general is not an attractive option since it will increase the number of children with disease-related deaths. In response to this clear need, the Collaborative WT Africa Project group started SUCCOUR, a project to improve supportive care for children with cancer in Africa. The vision of SUCCOUR is that all children with cancer in Africa will have the best supportive care to be cured from cancer. The project includes a nursing component, with funding for a ‘SUCCOUR’ nurse on the ward, who does clinical service and serves as a ‘role model’ for the key role of nurses in supportive care and monthly educational web meetings on supportive care. A baseline assessment of current practice and outcomes in four important areas of supportive care has been done to help decide which interventions need to get priority and to be able to evaluate impact.

Finally, 26% of our patients above age 6 months who had a nephrectomy had a relapse of disease compared to 13% in a similar cohort in the most recent SIOP renal tumour study group (RTSG) study. Late presentation and the absence of radiotherapy likely contributed to the high relapse rate in our study. This is supported by the finding that the relapse rate was higher (28%) in centres without radiotherapy and shorter postoperative chemotherapy than in centres with radiotherapy and longer postoperative chemotherapy (12%).

5 | CONCLUSIONS

This collaborative implementation of an adapted WT treatment guideline, using relatively simple and low-cost interventions, was feasible. Two-year EFS was almost 50%. In addition, a significant decrease in treatment abandonment and increase in survival at the end of treatment were observed compared to a pre-implementation cohort. Future work will focus on decreasing deaths during treatment and will include enhancing supportive care. The aim is to decrease both
abandonment of treatment and death during treatment to below 10%, and to increase survival of children with this common and curable tumour in sub-Saharan Africa to over 60%, in line with the Global Initiative for Childhood Cancer, launched by the WHO.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES
