CLINICAL PRESENTATION AND TREATMENT OUTCOME IN CHILDREN WITH NEPHROBLASTOMA IN KENYA

F. K. ABDALLAH and W.M. MACHARIA

ABSTRACT

Objective: To review the clinical presentation and management of children with nephroblastoma and the factors influencing the outcome at Kenyatta National Referral and Teaching Hospital (KNH).

Design: This was a retrospective case series study based on secondary data accumulated between 1990 and 1996.

Setting: The relevant data were extracted from records of all children aged 12 years and below, admitted for cancer at KNH, Nairobi.

Results: Out of 803 children with cancer, 71 (8.8%) had histologically proven nephroblastoma. At presentation, 1.5% were in stage I, 13.2% in stage II, 36.8% in stage III, 41.2% in stage IV and 7.4% in stage V. Eighty five per cent presented with stage III-V disease. Ninety five per cent had nephrectomy and received chemotherapy. Radiotherapy was given to 50.7% of the patients. Nine patients died before commencement of chemotherapy, two of whom died in the immediate post-operative period. The median duration between admission and surgery was 41 days. Pre-operative chemotherapy was given to 42% of the patients. Approximately 25.5% of the patients received little or no induction chemotherapy due to unavailability of drugs while only 2.8% received the prescribed maintenance treatment with the remainder getting erratic or no treatment. Overall, only 34.7% remained disease free two years from time of diagnosis.

Conclusion: Late presentation, poor availability of cytotoxic drugs and frequent treatment interruptions for various reasons have contributed to the poor outcome of nephroblastoma in Kenya.

INTRODUCTION

Nephroblastoma is the most commonly diagnosed childhood solid tumour in Kenya(1-3). Although the incidence in western Europe and the United States is similar, incidence rates in parts of Asia are lower than in Kenya while in Scandinavia they are slightly higher(4).

Survival (over two years) among children with nephroblastoma in developed countries increased from 26% after the second world war, when surgery was the only treatment, to 81% in 1980's after the addition of radiotherapy and actinomycin D. With the careful application of well designed multi-modal protocols in which combination chemotherapy has been used from the late seventies and eighties, the long term survival rose to over 80%(5,6).

Multi modal approach in the treatment of nephroblastoma was first used in Kenya in the early seventies(7) and comprised nephrectomy, single drug (actinomycin-D) adjuvant chemotherapy and radiotherapy. In situations where no specific management protocol was used, the outcome was poor. Later experience indicated that in a well organised setting, nephroblastoma is a potentially curable tumour provided it is diagnosed early and an aggressive multi-disciplinary management is adopted(1).

Kenya being a developing country, human and physical resources are not readily available, except at KNH where most of the cases of nephroblastoma are referred. However, KNH being a public hospital has limited supplies of chemotherapy, thus placing substantial economic constraints on the affected families since relatives have to buy these expensive drugs. The management of nephroblastoma at Kenyatta National Hospital (KNH) was last reviewed 16 years ago(1). This study was carried out to review the presentation, management and outcome status of children with nephroblastoma and to also identify factors influencing the outcome.

MATERIALS AND METHODS

Study design: This was a retrospective case series study of patients admitted at KNH over a period of seven years (1990-1996).

Materials: All files of patients admitted for management of nephroblastoma were reviewed. Pre-designed data extraction sheets were used to extract information.

Inclusion criteria: All children, up to the age of 12 years with a diagnosis of nephroblastoma.

Exclusion criteria: Those cases lacking a histological diagnosis were excluded from the study.
Ethical considerations: The identities of the patients used were kept confidential and not revealed in this study. The patients were not harmed in any way because of this study.

Availability of chemotherapeutic agents was assessed for each individual. This was possible because the treatment sheets used during the therapy are all found in the respective files including the nursing notes. If and when any drug(s) was not given, it would not be ticked on the said treatment sheet with a reason written next to it (e.g. low counts) and/or it would be explained in the notes. The ward doctors were quite explicit in giving the reason when any chemotherapeutic drug(s) was not given. The following definitions were used for assessing treatment:

**Good** - Most of the drugs given ≥ 75% of the time, especially actinomycin-D.

**Favor** - Most of the drugs given ≥ 50% of the time but <75%.

**Poor** - Drugs given ≤ 25% of the time, especially actinomycin-D.

Other definitions used:

- **Anaemia:** Six to ≤ 73 months old child, Hb ≤ 11g/dl
  - Seventy three to ≤ 168 months old child, Hb ≤ 12 g/dl

- **Leucocytosis:** WBC count > 16 x 10^3/L ≥ 48 months old child.
  - WBC count > 12 x 10^3/L > 48 months old child.

- **Neutropenia:** Absolute count ≤ 1000/mm³ neutrophils.

- **Thrombocytosis:** Platelet count > 450 x 10^3/mm³

- **Thrombocytopenia:** Platelet count ≤ 150 x 10^3/mm³

- **Blood biochemistry:** Normal range for age group is used.

- **Proteinuria:** Mild - + (<30 mg/dl protein).
  - Moderate - ++ (3-100 mg/dl protein).
  - Severe - ++++ (<300 mg/dl).

- **Haematuria:** RBC on urine microscopy or dip-stick (significant level > 3rbc/HPF)

Complications of therapy:

Infections - Temperature >37.8°C more than three occasions within six hours constituted pyrexia and was assumed to be due to infection.

**Haematological**
- Anaemia
- Neutropenia
- Thrombocytopenia

Data were screened for multiple entries and other errors before analysis and then describes using ratios or percentages and displayed in tables and charts. Comparison of frequencies was done using the Chi-square test.

RESULTS

Most of the patients studied were evaluated and managed at KNH. There were a few referred to KNH after initial evaluation and/or operation (nephrectomy) in provincial and missionary hospitals. Most of the follow up management were done in the haematology/oncology clinic of KNH but those who had not achieved remission and had a poor clinical condition were discharged to the hospitals nearest to their homes at the parents' request.

Treatment of the patients included surgery (nephrectomy), followed by chemotherapy. Those whose tumours were inoperable had fine needle aspirate or incisional biopsy for histological diagnosis before commencement of pre-operative chemotherapy (actinomycin D and vincristine) to shrink the tumour before finally undergoing nephrectomy. At surgery, the clinico-pathological staging of the tumour was done according to the US National Wilms' Tumour Study Committee. Post nephrectomy patients were given a six week course of induction chemotherapy consisting of vincristine, cyclophosphamide and actinomycin-D. The stage I-II (and sometimes III) received radiation of the tumour bed except those who were less than two years of age who were only followed up in the clinic. The stages III-IV were then given a second induction course (six weeks) followed by a full course of maintenance chemotherapy for 18 months consisting of the above three drugs with the addition of adriamycin which was alternated with actinomycin-D.

Any of the patients whose tumours recurred or metastatised were re-induced again using the same regimen, and if they went into remission, were put on maintenance treatment irrespective of disease stage. All the maintenance treatment except for the first was done on an outpatient basis.

Remission status for stage III-IV was assessed both clinically and using imaging techniques (chest x-ray and abdominal ultrasound). Once maintenance was completed, patients were followed up at increasing intervals at the clinic. During the treatment and follow up periods, the following parameters were monitored: full blood counts, liver function tests, serum electrolytes, urea and uric acid. Periodic chest x-rays and abdominal ultrasound were also done. If complications occurred at any time, the patients were re-admitted for inpatient care. Out of 803 admissions of children with various malignancies, 71 had nephroblastoma giving a relative frequency of 8.8% (95% CI=8.72, 8.96) (Table 1).

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>11 (15)</td>
</tr>
<tr>
<td>1991</td>
<td>9 (13)</td>
</tr>
<tr>
<td>1992</td>
<td>10 (14)</td>
</tr>
<tr>
<td>1993</td>
<td>10 (14)</td>
</tr>
<tr>
<td>1994</td>
<td>9 (13)</td>
</tr>
<tr>
<td>1995</td>
<td>12 (17)</td>
</tr>
<tr>
<td>1996</td>
<td>10 (14)</td>
</tr>
</tbody>
</table>

**Total** 71 (100)

The male to female ratio was 1:1.15. Their ages ranged from four months to 12 years, the median age being 48 months. Those below two years were 24.6% while 55% were in the two to five year age group and 20.3% in the five to twelve years (Figure 1) age group. All patients presented with an abdominal mass. The commonest ethnic group to which the patients belonged was the Kikuyu 44.3%, followed by the Kambas 14.1% and Kisii 12.7%.
At initial assessment, 64.8% were anaemic, 18.3% had leucocytosis, 37.9% thrombocytosis, 33.9% were uraemic, 23.6% had moderate to severe proteinuria and 28.2% had haematuria. None of the patients had positive vanillylmandelic acid (VMA) tests in their urine. Half of the patients had bone marrow aspiration for cytology and 29% turned out to be normal. Of the abnormal marrows, the commonest was a reactive picture followed by iron deficiency anaemia. The percentage of children with abnormal chest x-ray was 25.7%, where the majority (67%) had secondary tumour deposits. Abdominal ultrasound was done on 76% of the children, all of which showed renal masses, the left being more common (57.6%). Liver involvement occurred in 35% of those in stages IV and V. Intravenous urogram (IVU) showed the affected kidneys to be non functional in the majority of the patients (94.4%).

At laparotomy, 58 children (85.7%) were in advanced stages, most of whom (41.2%) were found to be in stage IV. Tables 2 and 3 show stage of disease against age and sex respectively.

### Table 2

<table>
<thead>
<tr>
<th>Age in months</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24</td>
<td>0 (0)</td>
<td>4 (5.9)</td>
<td>7 (10.3)</td>
<td>4 (5.9)</td>
<td>2 (2.9)</td>
<td>17 (25)</td>
</tr>
<tr>
<td>24-60</td>
<td>1 (1.5)</td>
<td>3 (4.4)</td>
<td>17 (25)</td>
<td>15 (22.1)</td>
<td>2 (2.9)</td>
<td>38 (55.9)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>0 (0)</td>
<td>2 (2.9)</td>
<td>1 (1.5)</td>
<td>9 (13.2)</td>
<td>1 (1.5)</td>
<td>13 (19.9)</td>
</tr>
<tr>
<td>Total</td>
<td>1.5</td>
<td>13.2%</td>
<td>36.8%</td>
<td>41.2%</td>
<td>7.4%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Of the patients in advanced stage, 89.5% were in the two to five year age group. The difference in age groups for the different stages was not statistically significant (p=0.47).

### Table 3

<table>
<thead>
<tr>
<th>Gender of patients by disease stage in percentages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex of patient</td>
</tr>
<tr>
<td>Disease stage</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>Early (I-II)</td>
</tr>
<tr>
<td>Late (III-IV)</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Though it seems that more girls than boys suffer from nephroblastoma, this difference is not statistically significant (p=0.20, Table 2).

Nearly all the children (68 (95%) had nephrectomy, while a few died before surgery could be scheduled. One patient died during surgery due to uncontrollable haemorrhage. Ninety eight per cent of these children received some chemotherapy while 50.7% received radiotherapy and chemotherapy. The median duration between onset of symptoms and establishment of the diagnosis was 92 days while 75% taking up to 125 days before a diagnosis could be made.

The median duration from diagnosis to surgery was 41 days with 75% taking up to 56 days. The median duration between diagnosis to start of chemotherapy was 38 days (75% taking up to 46 days). Those who had pre-operative chemotherapy (at least one dose of actinomycin D) were 42% with, the remaining (58%) receiving post-operative chemotherapy alone. Availability of drugs was a major problem especially in the maintenance period where only 22.5% had acceptable treatment (Table 4).

### Table 4

<table>
<thead>
<tr>
<th>Availability of chemotherapy in percentages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Availability grading</td>
</tr>
<tr>
<td>Good</td>
</tr>
<tr>
<td>Fair</td>
</tr>
<tr>
<td>Poor</td>
</tr>
<tr>
<td>Not given</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

*Patients in stage I and II were intentionally not put on maintenance treatment

Fifty per cent of the children developed therapy-related complications of which 50.7% were infections and 49.3% haematological. The commonest infections observed were bronchopneumonia (20%) and chicken pox (17.1%). Of the haematological complications, neutropenia (52.8%) was the commonest followed by pancytopenia (30.6%).

Fifty seven per cent of the patients with late stage diseases (III-V) attained complete remission. Twenty two per cent had partial remission while nine per cent died. Seven patients (12.1%) were lost to follow up (Table 5).
Table 5

<table>
<thead>
<tr>
<th>Age in month</th>
<th>Complete remission (%)</th>
<th>Partial remission (%)</th>
<th>Dead (%)</th>
<th>Lost to follow up (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 24</td>
<td>8 (13.8)</td>
<td>3 (5.2)</td>
<td>2 (1.8)</td>
<td>2 (3.4)</td>
<td>14 (24.2)</td>
</tr>
<tr>
<td>24-60</td>
<td>20 (34.5)</td>
<td>8 (13.8)</td>
<td>2 (3.4)</td>
<td>3 (5.2)</td>
<td>33 (56.9)</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>5 (8.6)</td>
<td>2 (3.4)</td>
<td>2 (3.4)</td>
<td>1 (1.8)</td>
<td>11 (18.9)</td>
</tr>
<tr>
<td>Total</td>
<td>33 (56.9)</td>
<td>13 (22.4)</td>
<td>5 (8.6)</td>
<td>7 (12.1)</td>
<td>58 (100)</td>
</tr>
</tbody>
</table>

Of the 33 children who attained complete remission in late stages, 20 (60.6%) were 24-60 months of ages. This age group contributed to less than half (39.2%) of the dead children. Remission status was not affected by the age of the patient in this study (p=0.47). Outcome of treatment was similar in males and females (p=0.20).

Table 6

| Stage | Disease free | 1 year | 2 years | | Outcome | Disease free | Dead/relapse | Disease free | Dead/relapse | Overall | Disease free | Dead/relapse | Overall |
|-------|--------------|--------|---------|-----|--------|-------------|--------------|--------------|-------------|------------|---------|-------------|-------------|---------|
| I-II  | 6 (85.8)*    | 5 (71.4)| 2 (28.6)| |       |             |              |              |             |           |           |             |             |         |
| III-V | 33 (72.6)    | 12 (28.6)| 3 (71.4)| |       |             |              |              |             |           |           |             |             |         |
| Overall| 39 (79.6)    | 17 (34.7)| 32 (65.3)| |       |             |              |              |             |           |           |             |             |         |

*Percentage shown in parentheses

Table 7

<table>
<thead>
<tr>
<th>Stage</th>
<th>Disease free</th>
<th>1 yr</th>
<th>2 yrs</th>
<th></th>
<th>Outcome</th>
<th>Disease free</th>
<th>Dead/relapse</th>
<th>Disease free</th>
<th>Dead/relapse</th>
<th>Total</th>
<th>Disease free</th>
<th>Dead/relapse</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24</td>
<td>9 (90)*</td>
<td>2</td>
<td>10</td>
<td></td>
<td></td>
<td>2 (20)</td>
<td>1 (10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>24-60</td>
<td>20 (74.1)</td>
<td>9</td>
<td>17</td>
<td></td>
<td></td>
<td>7 (25.9)</td>
<td>2 (75.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>27</td>
</tr>
<tr>
<td>&gt;60</td>
<td>10 (83.4)</td>
<td>5</td>
<td>15</td>
<td></td>
<td></td>
<td>2 (26.6)</td>
<td>5 (41.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>16</td>
<td>54</td>
<td></td>
<td></td>
<td>10 (26.6)</td>
<td>5 (41.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>49</td>
</tr>
</tbody>
</table>

*Percentage shown in parentheses

Approximately 38% of children experienced relapse. The majority relapsed (61.5%) within one year. The commonest site of relapse was the lungs (36.8%) followed by the liver (26.3%). Overall, 28.6% of the patients were disease free for more than two years while one patient is surviving disease free in the seventh year. Long term follow up has not been possible for majority of the patients.

DISCUSSION

The relative frequency of nephroblastoma of 8.8% among childhood cancers found in this study compares well with previous Kenyan studies(1,2). At one time it was thought that nephroblastoma had a constant incidence in the world. With the accrual of more data, it appears that although the incidence rates in parts of Asia are similar (Japan 4.0% and India 4.0%), the rate is lower compared to Scandinavia (Sweden 9.2%, Finland 10.0%)3. Variations in the incidence of nephroblastoma could reflect different gene pools or different environmental factors. It is also heartening to note that the incidence of this tumour in the age group 0-4 years is (74%)1,2,3,8. In the United States, about 75% of cases occur in children less than five years of age(10). The percentage of our patients who were over eight years was 11.3% though literature reports suggest nephroblastoma to be rare after this age(8,11).

The male:female ratio in this study showed a slight female predominance (1:1.15) as echoed by the latest Kenyan study(4) and one in the United States(10). Earlier Kenyan studies reported male predominance initially(4,7) and later an equality(1,2) as shown elsewhere in the world(4).

The ethnic distribution of nephroblastoma in this study was favouring the Kikuyu (44.3%) over the Kamba (18.6%) and the Kisi (14.3%) ethnic groups as in previously reported studies(2,7). This may reflect the proximity of KNH to the Central and Eastern provinces predominantly inhabited by the Kikuyu and Kamba respectively. The province with the third highest incidence is much further away from KNH. Other unexplained factors may therefore have a part to play.

In this study, the main reason for coming to hospital was an asymptomatic abdominal mass in all the patients as had been previously reported(2,4,7). The majority of the patients presented in hospital three months from detection of the abdominal mass. This delay in presentation is probably because of the initial asymptomatic nature of this disease as well as the fact that the normal habits of the young child is typically of a prounrerant abdomen, where an abdominal mass may grow to a large size before it is detected.

Delays in diagnosis may explain the late presentation of our patients with advanced disease, that is, stage III-V. Similar findings have also been reported elsewhere (9,10,12). At presentation, 64.8% of the patients were anaemic, compared to 22.2% in a previous study(2) perhaps because a higher percentage of patients (35.3%) with haematuria were seen in this study compared to the earlier report(7,9). Thrombocytosis (36.4%) was also common, partly explained by its known association with the presence of an abdominal mass. Increased erythropoietin production(13,14) may also have contributed though serum levels were not estimated in this study.

An elevated erythrocyte sedimentation rate (ESR) that became normal after nephrectomy was an expected feature as observed in 85% of the patients. Uraemia, which was observed in 33.9% of the patients with advanced
disease, was expected due to poor renal function. None of
the bone marrow aspirates showed any tumour cells; in
keeping with the observation of rare narrow involvement
in nephroblastoma(4,10). As expected, 92.4% of the
IVUs were reported to demonstrate non-functional kidneys,
while the remainder exhibited distorted calyceal systems.

Poor availability of drugs (chemotherapy) was
observed in 25.5% of the patients during induction and
52.9% in maintenance phases. These may partly be the
reasons for 45% of patients attaining only partial remission
or dying. Many of these children come from poor families
that live far from Nairobi so that when some of the
chemotherapy is not available at the hospital, many are
unable to contact the next of kin for their purchase. The
other reason may be the fact that 50% of these children
developed therapy-related complications which resulted
in interruption of their treatment thereby allowing further
tumour spread. These complications were almost equally
contributed to by infectious (30.7%) and haematological
(49.3%) complications. The infections consisted mostly
of bronchopneumonia and chicken pox due to both the
chemotherapy induced immunocompromised state and
neutropenia. The close interaction of the oncology patients
in an open ward may have resulted in increased risk of
contracting airborne infections. Possible simple measures
that can be taken to reduce these infective episodes would
be to have a ward with separate rooms for barrier nursing
and to put patients with neutropaenia on antimicrobial
prophylaxis. The haematological complications which
mainly comprised neutropenia (52.8%) and pancytopenia
(30.6%) were an expected effect of marrow suppressive
effects of chemotherapy. The long delays between onset
of illness to diagnosis (92 days) and from diagnosis to both
surgery (41 days) and chemotherapy (38 days) may also
have contributed to the poor outcome in a previous study(2).

Delays in treatment may have been contributed to by
several factors including the asymptomatic nature of the
disease, the unawareness of the parents on the seriousness
of the disease, inaccessibility and/or unavailability of
health services. Inability of the primary attending medical
officer to realise the need for urgency in the treatment of
nephroblastoma, inadequate diagnostic facilities, rapid
tumour growth, inadequate surgical facilities and
unavailability of some of the chemotherapeutic agents
may also have contributed to the delays.

The high relapse rate noted in this study may have
been influenced by delays in treatment. However, in spite
of all these problems, 55% were able to achieve complete
remission but only 28.6% of these patients were disease
free at two years. This compares well with previous
studies(1,2) in Kenya and other parts of the world(15,16).
Many of these children are alive today though some have
been lost to follow up.

In conclusion, despite the many difficulties
encountered in the management of cancers in a developing
country, treatment outcome for nephroblastoma at KH
has improved over the years. To improve compliance
during the maintenance phase of treatment and follow up,
It is recommended that a thorough family contact
information sheet be designed and put to use. Public health
education on occurrence of childhood cancers and
availability of effective treatment may further improve the
outcome. It also appears prudent that efforts be made to
mobilise further cancer treatment resources from the public
and private sectors. Further studies are also required to
determine cost effective treatment protocols most suitable
for the prevailing socio-economic environment.

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