Treating childhood acute lymphoblastic leukemia in Malawi

by George Chagaluka, Peter Carey, Kondwani Banda, Claire Schwab, Lucy Chilton, Ed Schwalbe, Roderick Skinner, Trijn Israels, Anthony Moorman, Elizabeth Molyneux, and Simon Bailey

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Paediatric acute lymphoblastic leukaemia (ALL) can now been cured in the vast majority of cases diagnosed in the developed world. However, the treatment regimes rely on good supportive care and multi-agent chemotherapy; and cannot be delivered in poor countries like Malawi. Thus many patients are left untreated. The difficulties in treating haematological malignancies in sub-Saharan Africa include a lack of medical resources (e.g. chemotherapy agents, supportive care, laboratory support), the inability of families to access basic services, and endemic infections. In 2010, the first Malawi ALL protocol was developed jointly by oncology teams in Malawi and the UK. As this was the first attempt to treat ALL in Malawi it was essential to set realistic goals and be mindful of the limited resources and infrastructure available. Therefore, the primary objective was to induce morphological remission, thereby allowing the children to go home clinically well and participate in normal life. The secondary objectives included delivering the protocol without excessive toxicity, monitoring outcome and sustaining remission. Based on our experience of treating Burkitt’s Lymphoma, we knew the following would be critical for successful implementation of the protocol: (1) length of hospital stay; (2) number of follow-up appointments; (3) toxicity, as measuring daily electrolyte levels and blood counts is not possible. Therefore the protocol was simple, short and only used drugs with proven anti-leukemic effect (Figure 1). The children were all hyperhydrated (3L/m^2/24 hours) and given allopurinol at the initiation of treatment in an attempt to reduce the risk of tumour lysis. Children with presumed infection or pyrexia were treated with intravenous antibiotics (initially penicillin and gentamicin) after excluding malaria. All children aged 1 to 16 years with morphologically diagnosed ALL were eligible for the protocol unless they had a life threatening infection or the family could not comply with the treatment and follow up. The study was approved by the local ethics committee in Blantyre and all families gave informed consent. Twenty patients (11 boys, 9 girls) with a median age 7.3 years were treated between December 2009 and August 2011 (Table 1). All children were tested for HIV status, only one was positive. The median haemoglobin concentration at diagnosis was 4.9g/dl, median white cell count (WCC) 41.6x10^9/L and median platelet count 18x10^9/L. Presenting history included prolonged bleeding (45%), nutrition (good 10%, fair 65%, poor 20% and kwashiorkhor 5%) and bone pain (35%). One patient had extensive lymphadenopathy. A total of 9 patients were screened by FISH for established chromosomal abnormalities; two were positive (ETV6-RUNXI and BCR-ABL1) but none had a MYC, MLL or IGH@ translocation.

Two children both with a high WCC died before treatment could be administered. A further seven patients died during induction therapy (Table 1). Among the 11 patients that completed induction all achieved a morphological remission by day 28. Maintenance therapy was well tolerated and two children completed therapy. Five children had presumed relapses during maintenance (3 confirmed by bone marrow examination) and 2 after completion of treatment (1 confirmed on bone marrow examination), all of whom died of their disease. One patient died of presumed bacterial meningitis during maintenance. There was no failure to complete treatment in those who did not relapse. The median time to death of those completing induction was 163 days (91-435). All but 2 patients relapsed during treatment. Three patients remain alive after 554, 232 and 93 days after treatment began. There was no relationship between outcome and white blood count, nutrition, overt bleeding, platelet count or bone pain.

We have demonstrated that it is possible to deliver ALL treatment in a resource limited setting. However, there is a period of intense learning as evidenced by the early death rate which was higher in the first 12 patients. Treatment efficacy may also be compromised by late presentation and relatively poor presenting condition. Our primary objective to deliver induction therapy and achieve a complete remission was achieved in 55% of patients, all of whom returned to their communities well and able to resume normal life albeit for some with a limited timeframe. We are continuing to develop this ALL protocol in realistic stepwise fashion. The second Malawi ALL protocol will have a 7day prednisolone pre-phase (to combat the high initial death rate) and 9
months of treatment (to lengthen remission duration). We are mindful that future protocols which should include more drugs will need to be accompanied by advances in supportive care.

Taking the first step to treat paediatric ALL is brave but important and our success should encourage others. Although the protocol was simple compared to those in the developed world, it is important that protocols evolve and develop in situ. Attempts to try and provide the same treatment as resource rich countries are likely to fail. Whilst it can be disheartening in the beginning many children who otherwise would die within days are now surviving for several months and we are now aiming to achieve a small number of long term survivors from the successor protocol.

*Dr George Chagaluka, Queen Elizabeth Hospital, Blantyre, Malawi; *Dr Peter Carey, Great North Childrens Hospital, Newcastle upon Tyne; Mr Kondwani Banda, Queen Elizabeth Hospital, Blantyre, Malawi; Ms Claire Schwab, Leukaemia Research Cytogenetics Group, Northern Institute for Cancer Research, Newcastle University, UK; Dr Lucy Chilton, Leukaemia Research Cytogenetics Group, Northern Institute for Cancer Research, Newcastle University, UK; Dr Ed Schwalbe, Northern Institute for Cancer Research, Newcastle University, UK; Dr Roderick Skinner, Great North Childrens Hospital, Newcastle upon Tyne; Dr Trijn Israels, VU Medical Center, Amsterdam, and Professor Anthony Moorman, Leukaemia Research Cytogenetics Group, Northern Institute for Cancer Research, Newcastle University, UK

**Professor Elizabeth Molyneux, Queen Elizabeth Hospital, Blantyre, Malawi.

**Professor Simon Bailey, Great North Childrens Hospital, Newcastle upon Tyne.

* equal contribution.

** equal contribution.

Correspondence

Simon Bailey, Great North Childrens Hospital, Newcastle upon Tyne, UK. Phone: international +44.191.2825395. Fax: international + 44.191.2824724. E-mail: simon.bailey@ncl.ac.uk
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The children and families in Malawi who bravely and with dignity face diseases such as ALL despite the many hardships they endure.

References.


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Table 1. Characteristics of ALL patients treated on the first Malawi ALL protocol.

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Age (y)</th>
<th>Sex</th>
<th>WCC x 10^9/L</th>
<th>Haemoglobin x g/dL</th>
<th>Platelets x 10^9/L</th>
<th>Genetic Analysis</th>
<th>Site of relapse</th>
<th>Current status</th>
<th>Survival (days)</th>
<th>Timing and cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.7</td>
<td>M</td>
<td>18</td>
<td>1.6</td>
<td>16</td>
<td>NAD</td>
<td>BM</td>
<td>Dead</td>
<td>141</td>
<td>Relapse - maintenance</td>
</tr>
<tr>
<td>2</td>
<td>8.7</td>
<td>F</td>
<td>14.5</td>
<td>4.3</td>
<td>8</td>
<td>Not tested</td>
<td></td>
<td>Dead</td>
<td>11</td>
<td>Induction - infection and bleeding</td>
</tr>
<tr>
<td>3</td>
<td>3.2</td>
<td>F</td>
<td>6.4</td>
<td>4.7</td>
<td>15</td>
<td>NAD</td>
<td>BM</td>
<td>Dead</td>
<td>435</td>
<td>Relapse - off treatment</td>
</tr>
<tr>
<td>4</td>
<td>4.4</td>
<td>F</td>
<td>17.0</td>
<td>5.9</td>
<td>249</td>
<td>Not tested</td>
<td></td>
<td>Alive</td>
<td>554</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2.5</td>
<td>F</td>
<td>21.0</td>
<td>5.5</td>
<td>16</td>
<td>Not tested</td>
<td></td>
<td>Dead</td>
<td>11</td>
<td>Induction - no obvious cause</td>
</tr>
<tr>
<td>6</td>
<td>9.0</td>
<td>F</td>
<td>107.8</td>
<td>3</td>
<td>2</td>
<td>Not tested</td>
<td></td>
<td>Dead</td>
<td>5</td>
<td>Induction - bleeding, dyspnea and pallor</td>
</tr>
<tr>
<td>7</td>
<td>1.9</td>
<td>M</td>
<td>24.7</td>
<td>4.2</td>
<td>148</td>
<td>NAD</td>
<td></td>
<td>Alive</td>
<td>232</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>12.1</td>
<td>M</td>
<td>88.0</td>
<td>5.8</td>
<td>17</td>
<td>Other abnormal</td>
<td></td>
<td>Dead</td>
<td>16</td>
<td>Induction - stridor and hypoxic</td>
</tr>
<tr>
<td>9</td>
<td>6.6</td>
<td>M</td>
<td>30.6</td>
<td>4.6</td>
<td>14</td>
<td>BCR-ABL1+ve in 22% cells</td>
<td>Dead</td>
<td>144</td>
<td>Maintenance - Infection (Bacterial meningitis)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>10.0</td>
<td>M</td>
<td>&gt;150</td>
<td>2.8</td>
<td>2</td>
<td>Not tested</td>
<td></td>
<td>Dead</td>
<td>1</td>
<td>Prior to treatment</td>
</tr>
<tr>
<td>11</td>
<td>12.0</td>
<td>F</td>
<td>86.0</td>
<td>3.7</td>
<td>10</td>
<td>Not tested</td>
<td></td>
<td>Dead</td>
<td>3</td>
<td>Prior to treatment</td>
</tr>
<tr>
<td>12</td>
<td>1.4</td>
<td>M</td>
<td>41.6</td>
<td>4.5</td>
<td>40</td>
<td>Not tested</td>
<td></td>
<td>Dead</td>
<td>17</td>
<td>Induction - no obvious cause</td>
</tr>
<tr>
<td>13</td>
<td>5.4</td>
<td>F</td>
<td>30.6</td>
<td>2.3</td>
<td>6</td>
<td>ETV6-RUNXI+ve in 84% cells; Loss of the native ETV6 allele was also present in 72% cells</td>
<td>Unknown</td>
<td>Dead</td>
<td>391</td>
<td>Unknown (Died in village) - but presumed relapse off treatment</td>
</tr>
<tr>
<td>14</td>
<td>1.4</td>
<td>F</td>
<td>83.6</td>
<td>5.9</td>
<td>19</td>
<td>Not tested</td>
<td></td>
<td>Dead</td>
<td>4</td>
<td>Induction - infection and hypoglycaemia</td>
</tr>
<tr>
<td>15</td>
<td>12.2</td>
<td>F</td>
<td>368</td>
<td>7.8</td>
<td>27</td>
<td>Not tested</td>
<td></td>
<td>Dead</td>
<td>19</td>
<td>Induction (Prednisolone only) – typhilitis and fever</td>
</tr>
<tr>
<td>16</td>
<td>15.2</td>
<td>M</td>
<td>260.8</td>
<td>7.5</td>
<td>23</td>
<td>NAD</td>
<td>BM and probably CNS</td>
<td>Dead</td>
<td>91</td>
<td>Relapse – on maintenance</td>
</tr>
<tr>
<td>17</td>
<td>2.4</td>
<td>M</td>
<td>280.0</td>
<td>6.6</td>
<td>35</td>
<td>NAD</td>
<td>Unknown</td>
<td>Died</td>
<td>190</td>
<td>Presumed Relapse (Died in Village) – on maintenance</td>
</tr>
<tr>
<td>18</td>
<td>14.3</td>
<td>M</td>
<td>78.8</td>
<td>6.4</td>
<td>99</td>
<td>Not tested</td>
<td>BM</td>
<td>Died</td>
<td>141</td>
<td>Relapse – on maintenance</td>
</tr>
<tr>
<td>19</td>
<td>14.8</td>
<td>M</td>
<td>56.0</td>
<td>5.1</td>
<td>20</td>
<td>Other abnormal</td>
<td>Unknown</td>
<td>Died</td>
<td>182</td>
<td>Presumed Relapse (Died in village) - on maintenance; CNS</td>
</tr>
<tr>
<td>20</td>
<td>8.0</td>
<td>M</td>
<td>2.5</td>
<td>6.1</td>
<td>29</td>
<td>Not tested</td>
<td></td>
<td>Alive</td>
<td>93</td>
<td></td>
</tr>
</tbody>
</table>

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Notes: (1) at presentation; (2) Genetic Analysis. Diagnostic samples were collected in preservative free heparin, fixed in methanol/acetic acid, stored at -20°C, batched and transported to Newcastle for analysis. All cases tested were screened by FISH (fluorescent in situ hybridization) for ETV6-RUNX1, BCR-ABL1 and rearrangements of the MLL, TCF3 (E2A), IGH@ and MYC genes using commercially available probes, according to the manufacturer’s instructions and as previously reported. Minimum of 100 interphase cells scored and independently checked by a second analyst. Abbreviations: BM – Bone Marrow, CNS – Central Nervous system, NAD – No abnormality detected.
Figure 1. Details of Treatment for the First Malawi ALL protocol

**Induction (4 weeks)**
- Cyclophosphamide – 300 mg/m\(^2\) day 1, IV
- Prednisolone – 40 mg/m\(^2\)/day x 28 days PO, then wean for 5 days
- Vincristine – 1.5 mg/m\(^2\) day 1, 8, 15, 22, 29, IV
- Intrathecal methotrexate – day 1, 7, 29, Intrathecal
- Septrin Prophylaxis for pneumocystis

Bone marrow examination at diagnosis and end of induction – verified by haematologist in Newcastle (PC). ((all slides, haematoxylin and eosin stained, were verified by a paediatric haematologist in Newcastle (PC))

**Maintenance (20 weeks)**
- Vincristine – 1.5 mg/m\(^2\) 4 weekly
- Prednisolone – 40 mg/m\(^2\)/day x 5 days 4 weekly
- 6-Mercaptopurine daily 60 mg/m\(^2\)
- Intrathecal methotrexate – 4 weekly
- Septrin prophylaxis for pneumocystis
- Monthly blood count
- Bone marrow at end of treatment