Treating childhood acute lymphoblastic leukemia in Malawi

Pediatric acute lymphoblastic leukemia (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. Therefore, many patients are left untreated. The difficulties in treating hematologic 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.[1] 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: i) length of hospital stay; ii) number of follow-up appointments; iii) toxicity, as measuring daily electrolyte levels and blood counts is not possible.[2,3] Therefore, the protocol was simple, short and only used drugs with proven anti-leukemic effect[4-7] (Figure 1). The children were all hyperhydrated (3 L/m 2/24 h) and given allopurinol at the

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

Patient ID	Age	Sex	WCC x 10⁹/L	Haemogloblin x g/dL¹	Platelets x 10⁹/L¹	Genetic Analysis²	Site of relapse	Current status	Survival (days)	Timing and cause of death
1	4.7	M	1.8	1.6	16	NAD	BM	Dead	141	Relapse – maintenance
2	8.7	F	14.5	4.3	8	Not tested		Dead	11	Induction – infection and bleeding
3	3.2	F	6.4	4.7	15	NAD	BM	Dead	435	Relapse – off treatment
4	4.4	F	17.0	5.9	249	Not tested		Alive	554	
5	2.5	F	21.0	5.5	16	Not tested		Dead	11	Induction – no obvious cause
6	9.0	F	107.8	3	2	Not tested		Dead	5	Induction – bleeding, dyspnea and pallor
7	1.9	M	24.7	4.2	148	NAD		Alive	232	
8	12.1	M	88.0	5.8	17	Other abnormal		Dead	16	Induction – stridor hypoxic
9	6.6	M	30.6	4.6	14	BCR-ABL1⁺ in 22% cells		Dead	144	Maintenance – infection (bacterial meningitis)
10	10.0	M	>150	2.8	2	Not tested		Dead	1	Prior to treatment
11	12.0	F	86.0	3.7	10	Not tested		Dead	3	Prior to treatment
12	1.4	M	41.6	4.5	40	Not tested		Dead	17	Induction – no obvious cause
13	5.4	F	30.6	2.3	6	ETV6-RUNX1⁺ in 84% cells. Loss of the native ETV6 allele was also present in 72% cells	Unknown	Dead	391	Unknown (died in village) – but presumed relapse off treatment
14	1.4	F	83.6	5.9	19	Not tested		Dead	4	Induction – infection and hypoglycemia
15	12.2	F	368	7.8	27	Not tested		Dead	19	Induction (prednisolone only) – typhlitis and fever
16	15.2	M	260.8	7.5	23	NAD	BM and probably CNS	Dead	91	Relapse – on maintenance
17	2.4	M	280.0	6.6	35	NAD	Unknown	Dead	190	Presumed relapse (died in village) on maintenance
18	14.3	M	78.8	6.4	99	Not tested	BM	Dead	141	Relapse - on maintenance
19	14.8	M	56.0	5.1	20	Other abnormal	Unknown	Dead	182	Presumed relapse (died in village) on maintenance; CNS
20	8.0	M	2.5	6.1	29	Not tested		Alive	93	

¹At presentation. ²Genetic 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.[8] Minimum of 100 interphase cells scored and independently checked by a second analyst. BM: bone marrow; CNS: central nervous system; NAD: no abnormality detected.
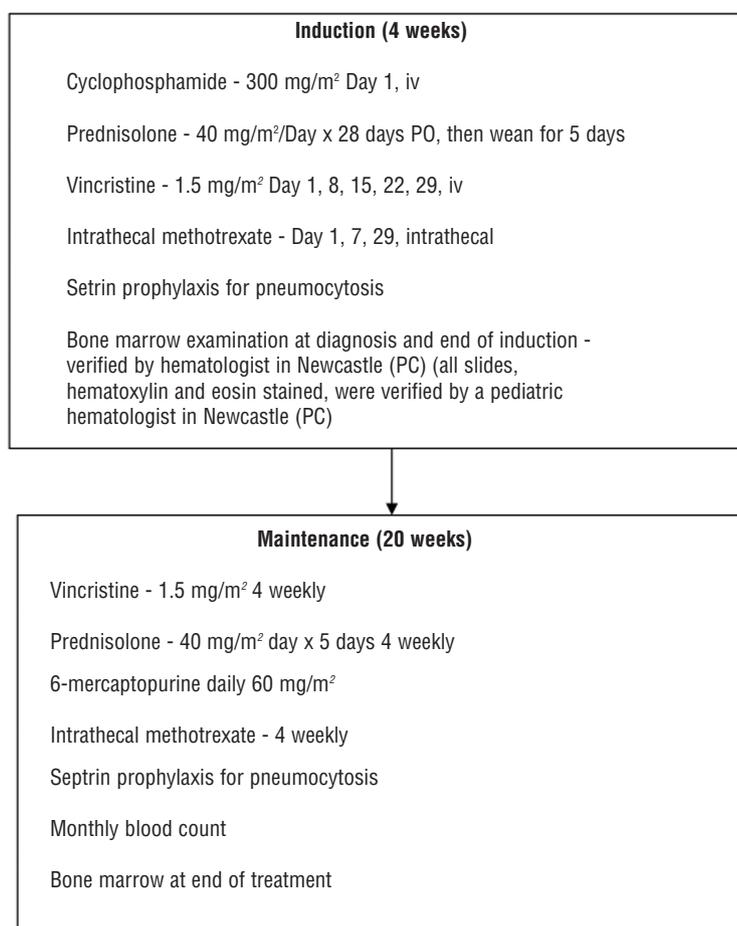
Induction (4 weeks)

Cyclophosphamide - 300 mg/m² Day 1, iv

Prednisolone - 40 mg/m²/Day x 28 days PO, then wean for 5 days

Vincristine - 1.5 mg/m² Day 1, 8, 15, 22, 29, iv

Intrathecal methotrexate - Day 1, 7, 29, intrathecal

Setrin prophylaxis for pneumocytosis

Bone marrow examination at diagnosis and end of induction - verified by hematologist in Newcastle (PC) (all slides, hematoxylin and eosin stained, were verified by a pediatric hematologist in Newcastle (PC)

Maintenance (20 weeks)

Vincristine - 1.5 mg/m² 4 weekly

Prednisolone - 40 mg/m² day x 5 days 4 weekly

6-mercaptopurine daily 60 mg/m²

Intrathecal methotrexate - 4 weekly

Septrin prophylaxis for pneumocytosis

Monthly blood count

Bone marrow at end of treatment

Figure 1. Details of treatment for the first Malawi ALL protocol.

initiation of treatment in an attempt to reduce the risk of tumor lysis. Children with presumed infection or pyrexia were treated with intravenous antibiotics (initially penicillin and genatamicin) after excluding malaria.

All children aged one 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 of 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 hemoglobin concentration at diagnosis was 4.9 g/dL, median white cell count (WCC) 41.6x10⁹/L, and median platelet count 18x10⁹/L. Presenting history included prolonged bleeding (45%), nutrition (good 10%, fair 65%, poor 20% and kwashiorkhor or 'swollen belly' 5%) and bone pain (35%). One patient had extensive lymphadenopathy. A total of 9 patients were screened by fluorescence *in situ* hybridization (FISH) for established chromosomal abnormalities; 2 were positive (*ETV6-RUNX1* 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 7 patients died during induction therapy (Table 1). Among the 11 patients that completed induction therapy, all achieved a morphological remission by Day 28. Maintenance therapy was well tolerated and 2 children completed therapy.

Five children had presumed relapses during maintenance (3 confirmed by bone marrow examination) and 2 after completion of treatment (one 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 (range 91-435). All but 2 patients relapsed during treatment. Three patients are still 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 low-resource setting. However, there is a period of intense learning as evidenced by the early death rate that 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 a realistic stepwise fashion. The second Malawi ALL protocol will have a 7-day 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 that should include more drugs will need to be accompanied by advances in supportive care.

Taking the first step to treat pediatric ALL is a brave move but an important one, 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. While 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 successive protocol.

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doi:10.3324/haematol.2012.071985

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