Compliance with chemotherapy in childhood leukaemia in Africa

L. G. MacDOUGALL, T. D. WILSON, R. COHN, E. N. SHUENYANE, S. E. McELLIGOTT

Summary

Compliance with chemotherapy in childhood leukaemia is usually good because of parental fear of the disease. However, poor compliance and refusal of treatment have been reported from both the USA and the UK. Little is known about African concepts of leukaemia, attitudes to treatment or compliance. A study was undertaken to investigate factors which might affect compliance in 15 black and 30 white families of leukemic children in Johannesburg. The socio-economic and educational status of the black families was lower than that of the white. Only 53% of black children attended hospital on the appointed day compared with 90% of white children. Less than 50% of black parents understood the nature of their child's illness. Both black and white families had unused medication at home. White parents more frequently reported toxic effects related to chemotherapy and more white children than black children exhibited lymphopenia during maintenance therapy. Assessment of drug compliance should be included as an independent variable when evaluating factors affecting response to chemotherapy in communities of diverse ethnic, socio-economic and cultural backgrounds.

Despite the improved prognosis in the past decade, childhood leukaemia is still viewed as a fatal illness in most westernised societies. It has therefore been assumed that compliance with chemotherapeutic regimens will be good because of parental anxiety. Only recently has this assumption been challenged and reports of poor compliance and refusal of treatment been recorded. In Third-World countries, little is known about parental concepts of childhood leukaemia and no compliance studies have been reported. Two brief reports suggest that the poor prognosis of childhood leukaemia in developing countries may be related in part to poor communication and irregular compliance with maintenance therapy.

Factors contributing to the poor prognosis for South African black children with acute lymphoblastic leukaemia (ALL) include age, central nervous system (CNS) disease at onset, FAB L2 or L3 morphology and irregular clinic attendance during outpatient maintenance therapy.

This latter observation raised the possibility that poor drug compliance might be an additional factor affecting prognosis. Good compliance is usually achieved when there is good patient/physician communication, understanding of the illness and positive attitudes towards treatment and outcome. Suboptimal compliance is more likely in socio-economically deprived families with multiple problems — poor interpersonal relationships, language or cultural differences with their physicians, complex drug regimens and incomplete understanding of the illness and aims of therapy.

A study was therefore designed to assess black and white parental concepts of childhood leukaemia, attitudes to therapy, educational and socio-economic status, understanding of information and instructions given at a clinic, and compliance with oral maintenance chemotherapy.

Subjects and methods

Families selected for interview were those with a child with leukaemia or lymphoma who had completed induction, consolidation chemotherapy and CNS prophylaxis and had been on oral maintenance or re-induction therapy for 3–12 months or longer. To avoid possible language or cultural barriers, white families were interviewed by a bilingual (English/Afrikaans) white research assistant (S.E.M.) and black families by a black social worker (E.N.S.) fluent in the languages most commonly spoken by the parents.

The interview was conducted from a structured questionnaire which had both closed and open-ended questions and provided for cross-checks on responses.

The major categories covered by the questionnaire were:

(i) home background; (ii) educational background and occupation of parents; (iii) understanding of the child's illness; (iv) clinic-related attitudes and problems; (v) understanding and administration of medications; and (vi) alternative sources of therapy or support. In addition to the questionnaire, a record was kept of clinic appointments, failure to attend on the correct date and the reasons given for default. White blood cell (WBC) counts, neutrophil and lymphocyte counts were monitored in patients with ALL on maintenance therapy with 6-mercaptopurine (6MP) and methotrexate (MTX). The desired range for total WBC during maintenance therapy was 2.0–3.5 x 10^9/l, with neutrophil and lymphocyte counts of 1.0 x 10^9/l or greater. The drug dosage prescribed at each clinic visit was recorded and the parent questioned at the time of the interview regarding the number and type of pills currently being given to the child.

Results

Fifty-five families were interviewed — 30 white and 15 black. No significant differences were found in the age and sex distribution between the two groups. The majority of the children (25 white and 11 black) had ALL or non-Hodgkin's lymphoma with leukemic transformation. The remainder had acute non-lymphoblastic leukaemia (ANLL). Over 80% were in remission at the time of the interview.

Socio-economic and educational background

White parents had fewer children than blacks (mean 2.5 ± 1.2 v. 3.8 ± 2.3, P = 0.05), fewer individuals per household (4.5 ± 1.6 v. 7.2 ± 3.1, P = 0.001) and more living space.
Although 90% of white and 80% of black parents were married, 60% of black mothers were functioning as ‘single parents’ because the fathers lived and worked apart from their wives and families. Two of the black families had incomes below the minimal subsistence level whereas no whites were in this category.

Of the 30 white mothers, 28 (93%) had completed secondary school, and 17 (57%) had matriculated. Only 7 black mothers (47%) had education beyond primary school and 3 (21%) had matriculated. Thirty per cent of mothers in both ethnic groups were employed full-time or part-time, with most white mothers in skilled and black mothers in unskilled employment.

All the white fathers were in skilled, business or professional employment compared with 54% of black fathers.

Twenty per cent of both white and black parents employed a maid or child-minder to care for preschool children during the day.

Of the school-age children in both ethnic groups, all but 1 were attending school regularly.

**Understanding of the illness**

With 3 exceptions (1 white, 2 black), all parents interviewed indicated that they had been informed about their child’s illness in a language that they understood. Many white parents augmented this information by reading books provided by the clinic. No such publications were available in African languages. The black families therefore received all their information by oral communication from the staff at the Haematology/Oncology Clinic.

All but 1 of the white parents understood that their child had leukaemia and appreciated the implications of this diagnosis. Those whose child had ANLL were aware that this was different from the more common ALL and was more difficult to treat. Most of the black parents had never heard of the disease leukaemia before their child was affected. Some were familiar with the term cancer, others were not. Explanations about the nature of cancer and leukaemia were therefore difficult and often unsuccessful. At the time of the interview only 7/15 of the black parents (47%) gave the interviewer the correct diagnosis of their child’s illness. Three parents indicated that they did not know the diagnosis or felt that there was nothing wrong with the child. Others stated that the child had worms, fits or toothache, these being the symptoms most recently noted. One mother considered her child to be bewitched. The majority of black parents knew that the doctors considered the child’s illness to be serious and required long-term treatment. Only 43% of black parents compared with 88% of whites understood why it was necessary to continue treatment when the child was in remission.

**Clinic-related information**

More black than white parents (53% v. 18%; P < 0.05) had problems in bringing the child to clinic, despite the fact that all needy families receive reimbursement for travel costs incurred. Reasons for default included poor transport facilities, distance from clinic, travel expenses, loss of a day’s wages and nobody to care for the other children on clinic days.

Ninety per cent of white parents stated that they had never missed a clinic appointment. Clinic records confirmed this figure. Eighty-seven per cent of black parents also stated that they never missed a clinic appointment. However, clinic records showed that only 8/15 (53%) came to clinic on the correct day. Two families who came to clinic several weeks late did not view this as having missed an appointment. The other 5 required social-worker home visits or contact with their employers before they returned to clinic. All parents indicated that they would have come to the clinic sooner if the child had appeared sick.

**Alternative sources of treatment or support**

A wide variety of medical, paramedical, religious and unorthodox sources of advice were sought by 87% of white and 80% of black parents. White families sought mainly religious help (77%) rather than alternate medical or paramedical advice (30%). Homeopathic remedies were occasionally used in conjunction with chemotherapy. In no instances did parents use ‘unorthodox’ cancer cures.

Eight black parents (53%) sought help from private doctors, local clinics or traditional healers if the child appeared sick. Seven of the black families (47%) also sought advice from religious leaders or faith healers. Some traditional healers advised the parent to take the child back to the hospital, others prescribed enemas, gave the child coal ash to eat or prescribed medication to add to the bath water.

**Medication**

Information regarding medication was obtained from 34 parents (24 white, 9 black) whose children were on regular maintenance therapy with oral 6MP and MTX. In most instances medication was given by the mother. Two teenage children took responsibility for their own medication. Instructions regarding drug administration were given verbally by a member of the clinic staff and/or the pharmacist. Instructions were also written on the pill container.

At the interview, the parents were asked to read the pharmacy instructions written on 3 different pill containers and were also asked how and when they gave 6MP and MTX to their own children. All the white parents could read the pharmacy instructions correctly and gave the correct response regarding the number and type of pills that their own child had been prescribed. Two of the 9 black parents were able to read all the written pharmacy instructions correctly. However, 8/9 black parents correctly remembered the verbal instructions regarding medication dosage and timing. Approximately 30% of both black and white parents stated that they occasionally forgot to give their child his tablets. Seventy-six per cent of white parents and 44% of black parents indicated that they still had unused medication at home at the time of their next clinic visit.

**Drug toxicity.** Significantly more white (16/24) than black (2/9) mothers reported drug toxicity while their children were on maintenance chemotherapy. The predominant symptoms attributed to the drugs were gastro-intestinal.

**White blood cell count**

All black children received induction, consolidation and cranial prophylactic therapy under medical supervision as inpatients due to parental transport problems. The majority of white patients received this therapy as outpatients after an initial brief period in hospital. Both ethnic groups received their maintenance therapy on an outpatient basis.

The WBC, neutrophil and lymphocyte counts were recorded at completion of induction, consolidation and CNS prophylaxis and during maintenance therapy. The mean WBC count was lower in black children (5.13 x 10^9/l) than white (7.70 x 10^9/l) after induction therapy, but the difference was not statistically significant. However, the mean lymphocyte count in blacks (1.26 x 10^9/l) was significantly lower than in whites (2.37 x 10^9/l; P = 0.05).

The number of episodes of leukopenia, neutropenia or lymphopenia before and during maintenance therapy is shown
in Table I. On completion of induction, consolidation and CNS prophylaxis, significantly more black children had WBCs less than 5,0 x 10^9/l, and lymphocyte counts less than 1,0 x 10^9/l. No blacks exhibited neutropenia. Less than 10% of whites were either neutropenic or lymphopenic.

After 6 weeks on maintenance therapy the situation was reversed. The WBCs of whites were more often in the desired range of 2-3,5 x 10^9/l than those of blacks, although the differences were not statistically significant.

However, whites had significantly more episodes of lymphopenia after 6 weeks of maintenance therapy than blacks. A similar picture prevailed at 12 weeks. Episodes of neutropenia were less common and occurred with equal frequency in blacks and whites. Cessation of maintenance therapy and administration of re-induction pulse therapy with vincristine and prednisone resulted in an increase in WBC and reversal of the lymphopenia in both blacks and whites.

Discussion

This study revealed significant differences in understanding of the illness and compliance with clinic attendance for continuation of chemotherapy between white and black parents of leukaemic children.

Factors known to contribute to poor compliance were more prevalent in black families than in white. Educational, language and cultural differences between black families and the medical staff posed problems in direct communication between doctors and patients. Although all black parents were counselled repeatedly in their home language by black nursing staff and social workers, this did not appear to help many of them understand the nature of the illness or the aims of therapy. The need to continue medication when the child appeared well was not a concept readily understood by black parents. Bringing a 'well' child to hospital on a specified day did not rank as a top priority when it involved financial outlay on bus fares or loss of a day's wage.

White parents did understand the implications of their child's illness, feared the possibility of a relapse and accepted the need for regular clinic attendance and prolonged treatment. The accumulation of unused tablets at home was the rule rather than the exception in both ethnic groups. The potential hazard of this store of toxic medication in the homes of families with no clear understanding of the nature of these drugs is a cause for concern.

The reasons for the higher incidence of reported drug toxicity in white children than in blacks is difficult to assess. Most white parents were aware of potential drug toxicity and therefore adverse symptoms might be recognised more quickly and attributed to the medication. Two possible reasons for the low incidence of reported toxicity in black children were given by the black social worker. Firstly, it might be considered inappropriate to imply that medical treatment had made the child ill. Alternatively, it was often appreciated that serious illnesses required 'strong treatment' and the ill-effects of the treatment were accepted as part of the cure. Differences in the reported incidence of toxicity between whites and blacks might also represent differences in compliance with chemotherapy.

Although there is not always good correlation between drug dosage and WBC count, monitoring the WBC remains the most practical means of assessing the haemopoietic effect of chemotherapy. In this survey, white children exhibited more episodes of lymphopenia during maintenance therapy than did black children, suggesting either poor compliance on the part of blacks or differences in drug metabolism. It is obvious that evaluation of response to chemotherapeutic regimens is meaningless if there is doubt as to compliance with medication. The reasons for the present poor survival rate in black children with leukaemia must therefore be addressed from several different angles: (i) it may be due to the greater prevalence of poor prognostic leukaemic subtypes in the black childhood popula­tion; (ii) it is evident that black parental understanding of the illness and aims of treatment are poor, therefore a more effective means of communication and education must be developed to ensure optimal compliance with drug regimens; (iii) outreach programmes are urgently required to provide assistance for working and 'single' parents to enable them to bring their children to clinics for regular follow-up; (iv) an accurate measure of drug compliance by means of serum or urine assays would be a major advance; and (v) it seems imperative that assessment of drug compliance should be included as an independent variable when evaluating factors affecting response to chemotherapy in communities with diverse socio-economic, ethnic and cultural backgrounds.

This survey was supported in part by the South African Medical Research Council, the National Cancer Association of South Africa, and the Samuel and Sylvia Schnaid Foundation.
Level of termination of the spinal cord during normal and abnormal fetal development

S. GOVENDER, R. W. CHARLES, M. R. HAFFEJEE

Summary

The level of termination of the spinal cord in 115 autopsies on subjects ranging from a 20-week stillborn to an 8-month-old infant is reported. The study showed that the adult level (lower border L1) is attained at birth. In a clinical study of 10 children with diastematomyelia between the ages of 3 years and 7 years the spinal cord, which was found to terminate in the region of the lower lumbar spine, was tethered by a short thickened filum terminale.

Interest in the level of termination of the spinal cord during normal fetal development arose from observations in diastematomyelia where the spinal cord terminates at the level of the lower lumbar vertebrae. Apart from minor racial and sexual variations, the spinal cord in the adult usually terminates at the lower border of the first lumbar vertebra.1

In reviewing reports on the level of termination of the spinal cord at birth, considerable controversy was found. Grant2 and Cunningham3 state that the cord terminates at the level of the 3rd lumbar vertebra, whereas Crossby4 et al. and Morris5 report that the cord terminates opposite the lower border of the 2nd lumbar vertebra. In a large postmortem study, Barson6 found that the cord terminates at the level of the 1st lumbar vertebra approximately 2 months after birth. Kunitomo,7 in describing the formation of the filum terminale, states that there is a mechanical disproportion between the growth of the vertebral column and the neural tube in fetal life. However, he did not determine the rate of differential growth. Streeten8 described the extent of the caudal displacement of the vertebral column relative to the position of the ventriculus terminalis and the attachment of the sacral nerves to the spinal cord at various stages in prenatal life.

Subjects and methods

One hundred and fifteen dead infants with ages ranging from 20 weeks' gestation stillbirth to 8 months old were included in this study. The major cause of death in the neonatal group was bronchopneumonia and gastro-enteritis. Fetal maturity was assessed from the mother's last menstrual period. Stillborns and infants with obvious congenital anomalies and those stillborns where the mother's last menstrual period was not known were excluded from this study. The autopsies were performed within 24 hours after death. The infants were placed in the prone position with the hips and knees fixed and the abdomen was supported with a cushion to maintain lumbar lordosis. The lower dorsal spine, including the 11th and 12th ribs and the entire lumbosacral spine, was exposed through a midline longitudinal incision. The dura was split longitudinally to expose the spinal cord after the posterior elements were removed. The junction between the conus medullaris and ventriculus terminalis was identified; this point marked the termination of the spinal cord (Fig. 1). The filum terminale, a continuation of the ventriculus terminalis, was also identified. The point of termination of the spinal cord was correlated to the nearest vertebral body or the midpoint of the vertebral body.