frequent intervals, certainly not less often than yearly, will result in an overall improvement in results. Despite generalizations about the approach, management for individual patients will require specific variations according to the child's and his family's special circumstances.

We wish to extend our gratitude to the Murray Trust for continued support of the Cleft Palate Unit at Red Cross War Memorial Children's Hospital, Cape Town.

REFERENCES


5. Spriesterbach, J. C., Dickson, D., Clarke Fraser, F. et al. (1973): Cleft Palate J., 10, 11.


Childhood and Adult Acute Leukaemia in Johannesburg Blacks

B. KUSMAN, R. J. JACOBSON, L. G. MACDOUGALL

SUMMARY

Thirty-four Black patients (14 children and 20 adults) suffering from acute leukaemia were assessed at the haematology clinics of Baragwanath Hospital and Johannesburg General Hospital during a recent 2-year period. It is evident that acute leukaemia in Blacks has become more prevalent in the Johannesburg area than it was 20 years ago, the increase being most striking in the younger age group. The incidence of acute myelocytic and lymphocytic leukaemia in Black children was the same. In adults acute myelocytic leukaemia predominated.

The remission rate of 90% achieved in patients with acute lymphoblastic leukaemia was similar to the rates described in Europe and the USA. Results in patients with acute myelocytic leukaemia were less favourable (35% with initial complete remission). The problems of management (limited isolation facilities), complications related to prolonged hospitalization (loss of earnings, problems of visiting), and difficulties with follow-up examination are outlined. In underdeveloped and developing countries, training paramedical personnel to assist with the outpatient care of patients with neoplastic disease might alleviate some of these problems.


Reports from tropical Africa reveal that the diagnosis of leukaemia has been made more frequently among Blacks during the past decade than previously. This increase may largely be due to an improvement in diagnostic facilities in these countries.

Only two detailed studies of acute leukaemia in Blacks have been reported from Johannesburg, both over 20 years ago. Grieg reported 14 cases of acute leukaemia diagnosed between January 1954 and December 1955, and Higginson and Oettle observed 24 patients during the 3-year period January 1953 – December 1955. In a study of cancer patterns in Blacks at Baragwanath Hospital over the years 1948 – 1964, leukaemia was underestimated because haematological results were not always available for scrutiny.

In the ensuing 20 years, the Johannesburg Black population has become more urbanized, medical services have expanded and more specialized facilities have become available. It seemed appropriate, therefore, to review the current status and therapy of acute leukaemia in this population group.
PATIENTS AND METHODS

All Black patients with acute leukaemia seen at the haematology clinics of Baragwanath Hospital and Johannesburg General Hospital from 1 October 1973 to 30 September 1975 were entered into this study. Both hospitals served as principal medical centres for approximately 800 000 Blacks living in Johannesburg and the surrounding townships (Population Census, 1970). Patients were initially admitted to hospital for diagnostic studies and initiation of therapy. The diagnosis of leukaemia was confirmed by examination of peripheral blood and bone marrow aspirates, and in some instances by bone marrow trephine or lymph node biopsy.

In patients with acute lymphoblastic leukaemia, bone marrow aspirates showed moderate to almost complete replacement with primitive lymphoblasts. Cytotoxic staining was applied in a few of these cases and all were PAS-positive. In the non-lymphoblastic leukaemias, the term myeloblastic was applied to the morphological varieties now categorized in the French-American-British (FAB) classification as M1, M2, and M4.\(^4\) Acute progranulocytic leukaemia was equivalent to FAB M3, acute monocytic leukaemia to M5, and erythroleukaemia to M6.

The myeloperoxidase and naphthol AS-acetate esterase reactions and Sudan black staining were used to assist in differentiating myelocytic and monocytic varieties.

All patients had the benefit of general supportive care, intravenous fluids, blood and platelet transfusions and antibiotic therapy when indicated. Strict isolation was rarely possible, and the majority of patients were nursed in open wards. Allopurinol was always given before chemotherapy.

Chemotherapy

Acute myeloblastic leukaemia (monocytic, progranulocytic and erythroleukaemia). For the induction of remission daunorubicin 1.5 mg/kg was given intravenously on the 1st day and cytosine arabinoside 1.0 mg/kg was administered intravenously 12-hourly on days 1 - 5. The above course was repeated every 5 - 7 days until remission had been achieved (maximum 6 courses).

For CNS prophylaxis cranial irradiation with 2400 rad was given as well as intrathecal methotrexate 12 mg/m\(^2\) twice weekly for 5 days. This therapy was only given to patients in whom complete haematological remission had been achieved.

Maintenance therapy was as follows: daunorubicin and cytosine arabinoside as for remission induction, continued for 3 further courses, followed by the following, monthly: vincristine 2 mg/m\(^2\) intravenously on the 1st day, cyclophosphamide 100 mg/m\(^2\) by mouth on days 1 - 5, cytosine arabinoside 100 mg/m\(^2\) intravenously on days 1 - 5, and prednisolone 100 mg twice daily by mouth on days 1 - 5, or thioguanine 60 mg/m\(^2\) by mouth daily.

Acute lymphoblastic and stem cell leukaemia. For the induction of remission vincristine 2 mg/m\(^2\) was administered intravenously weekly for 3 weeks and prednisone 40 mg/m\(^2\) by mouth daily for 3 weeks. If remission had not been achieved by this time, intravenous daunorubicin 1.5 mg/kg weekly was added to the induction regimen and continued for a further 3 weeks.

For CNS prophylaxis cranial irradiation with 2 400 rad was given and intrathecal methotrexate 12 mg/m\(^2\) on alternate days for 6 days.

Maintenance therapy was as follows: 6-mercaptopurine 50 mg/m\(^2\)/d by mouth, methotrexate 20 mg/m\(^2\) by mouth weekly and cyclophosphamide 200 mg/m\(^2\) by mouth weekly.

Systematic reinduction (every 10 weeks) was as follows: vincristine 2 mg/m\(^2\) intravenously weekly for 3 weeks and prednisolone 40 mg/m\(^2\) by mouth for 2 weeks.

Most of the patients were given prophylactic antituberculous therapy (isoniazid) because of the high incidence of latent tuberculosis in Black patients in Johannesburg.

RESULTS

Thirty-four patients were seen during the 2-year period (20 adults and 14 children aged 1 - 15 years). Of the 14 children, 6 had acute lymphoblastic leukaemia, 5 had acute myeloblastic leukaemia, and there was 1 case each of acute monocytic, progranulocytic and undifferentiated stem-cell leukaemia. The adult acute leukaemias comprised 4 cases of acute lymphoblastic leukaemia, 12 of acute myeloblastic leukaemia, 2 of acute monocytic leukaemia, and 1 case each of acute undifferentiated stem-cell leukaemia and acute erythroleukaemia. The age and sex of the patients and type of leukaemia are illustrated in Table I. The mean age of the children was 5.9 years and that of the adults 32 years. Seventeen were young adults and only 3 were over 50 years. In patients with acute lymphoblastic leukaemia the mean age for children was 3.5 years and that for adults 32.5 years. In patients with acute myeloblastic leukaemia the mean age for children was 6.3 years and that for adults 32.3 years.

In the 1 - 15-year age group there were 8 boys and 6 girls (M : ratio = 1.3 : 1) and in the adult group 11 males and 9 females (M : F ratio = 1.2 : 1).

The children presented most commonly with severe anaemia (64.3%), bone and joint pains (46%), fever and/or obvious infection (46%) and bleeding manifestations (38.5%). Lymphadenopathy and hepatosplenomegaly were not prominent features and were present in only 23 - 30% of cases. In adults the most common presenting features were bleeding manifestations (75%), hepatomegaly (55%), lymphadenopathy (50%), infections (50%), severe anaemia (42%), generalized pain, weakness and shortness of breath (35%).

Of the 14 children, 11 were anaemic on admission (Hb < 10 g/dl) and in 9 the anaemia was severe (Hb < 7 g/dl). Of the adults, 14 out of 19 were anaemic and in 8 the anaemia was severe.

The total white blood cell count in adults and children with acute lymphoblastic or stem-cell leukaemia ranged from 1 900 to 18 300/μl. Leucocytosis was characteristic of the myeloblastic and monocytic leukaemias in children; in adults with these leukaemias, extremes of leucocytosis and leucopenia were encountered. The majority of patients were thrombocytopenic.
The response to therapy and survival are shown in Table II. Complete remission was achieved in 9 of the 10 patients with acute lymphoblastic leukaemia and partial remission in 1 adult. Of the 4 adults, 2 died within 1 week of institution of therapy. The other 2 remained in remission for 5 and 11 months and were then lost to follow-up examination.

Of the 6 children with acute lymphoblastic leukaemia, 2 have been maintained in continuous haematological remission for 31 and 36 months and are still on maintenance therapy. One child was maintained in haematological remission for 25 months and then relapsed. Despite intensive reinduction therapy with vincristine, daunorubicin, cyclophosphamide, 'high-dose' methotrexate, L-asparaginase, and adriamycin in varying combinations, it was not possible again to achieve remission. The patient died 28 months after the initial diagnosis. In 3 children, follow-up examination was erratic and maintenance therapy was given irregularly. All 3 relapsed within 8 - 16 months of diagnosis. After intensive reinduction therapy a partial remission was achieved in 1 patient and no response in the other 2. These 3 children died 15, 16 and 30 months respectively after the initial diagnosis.

Of the 17 patients with acute myeloblastic leukaemia, complete remission was achieved in 6, partial remission was achieved in 6, and 5 adults died within 1 week of institution of therapy.

Of the 4 adults in whom complete remission was achieved, 2 relapsed and died after 6 and 13 months. Two were still in remission 14 and 20 months after initiation of therapy and were then lost to follow-up examination. The 3 patients in whom partial remission was achieved were still on therapy 10 - 18 months later.

The 2 children in whom complete remission was achieved relapsed after 5 months of therapy. Further reinduction therapy was unsuccessful and both children died 7 months after the initial diagnosis. Three children in whom partial remission was achieved survived for 7, 8 and 10 months before succumbing to intractable infections.

In none of the patients with acute monocytic or progranulocytic leukaemia, erythroleukaemia or stem-cell leukaemia was remission achieved, and all but 1 died within 4 months of diagnosis.

| TABLE II. RESPONSE TO THERAPY AND SURVIVAL IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKAEMIA AND ACUTE MYELOBLASTIC LEUKAEMIA |
|---------------------------------------------------------------|---------------------------------------------------------------|
| Classification                                               | Children (1 - 15 yrs)                                         | Adults (>16 yrs)                                            |
|                                                              | Number of patients | Remission | Survival (mo.) | Number of patients | Remission | Survival (mo.) |
| Acute lymphoblastic leukaemia                                 | 6                 | 6 CR      | 2 CR at 31 and 36 mo. | 4                 | 3 CR      | 1 died in relapse at 11 mo. |
|                                                              | 1 relapsed at 25 mo., died at 28 mo. | 1 relapsed at 8 - 16 mo., died at 15, 16 and 30 mo. | 2 lost to follow-up at 5 and 11 mo. | 1 PR      | 1 died at 11 mo. |
| Acute myeloblastic leukaemia                                  | 5                 | 2 CR      | 2 relapsed within 5 mo., died at 7 mo. | 12                | 4 CR      | 2 relapsed, died at 6 and 13 mo. |
|                                                              | 3 PR      | 3 died at 7, 8 and 10 mo. | 2 lost to follow-up at 14 and 20 mo. | 3 PR      | 3 alive at 10 - 18 mo. |
|                                                              |                 |           | 5 died within 1 wk |                  |           |                              |

CR = complete remission: <5% blasts in the bone marrow with normal distribution; and PR = partial remission: >5% but <30% blasts in the bone marrow.
DISCUSSION

From the present observations it appears that acute leukaemia in Blacks may have become more prevalent in the Johannesburg area than it was 20 years ago. The increase has been most notable in the youngest age group. Of the 14 children with acute leukaemia seen during the 2-year period, 8 were under 5 years of age. This is in sharp contrast to the report of Grieg, who encountered no children under 5 years of age with acute leukaemia, and Higginson and Oettle, who reported only 8 patients under 10 years of age in a 3-year study of 63 patients with both acute and chronic leukaemia. Reports from West, Central and East Africa have also referred to the rarity of acute leukaemia in Black children, particularly in those under 5 years of age. In both Rhodesia and Nigeria the peak childhood incidence was in the 7-15-year age group.

The emergence of acute leukaemia in young Blacks in Johannesburg conforms more closely to the pattern seen in Western countries where the peak incidence is in the 3-5-year age group, but the cytological distribution is different from that seen in Western countries in that 50% of the cases were myelomonocytic. A similar incidence of acute myelomonocytic leukaemia in childhood has also been reported from Kenya, Uganda and Rhodesia. The apparent increase in acute leukaemia in the Johannesburg area is probably due to several factors, among which are improved medical facilities and increased referral of patients to specialized centres for diagnosis and treatment.

In adults, acute leukaemia was more common under 40 years of age and, again, the most common type was myelocytic. The mean age for patients with acute lymphocytic and also for those with acute myelocytic leukaemia was 32 years. The male preponderance among both children and adults was similar to that noted in other countries.

In the present series there were notable differences in clinical presentation between children and adults. Children mostly presented with severe anaemia, bone and joint pains and infections. The incidence of lymphadenopathy and hepatosplenomegaly was unexpectedly low. In adults the most common presenting features were haemorrhage, hepatomegaly, lymphadenopathy, infection and anaemia.

In patients with acute lymphoblastic leukaemia the initial response to chemotherapy was good. Complete remission was achieved in 90% of patients, a figure which compares favourably with results obtained with similar chemotherapeutic regimens in specialized centres in Western Europe and the USA. The relatively short first remission achieved in 3 children was probably due to failure to comply fully with maintenance therapy. Compared with our experience with White children, the inability to induce complete remission again in any of the Black children was unusual. From the small number of patients observed so far, it is impossible to determine whether this is a common feature in South African Blacks with acute lymphoblastic leukaemia. In patients with acute myeloblastic leukaemia initial complete remission rates (35%) were less favourable than the best achieved (50-79%) in other more specialized centres. The more favourable remission rates described in childhood acute myeloblastic leukaemia compared with those in adults were not evident in the present series.

Inherent difficulties were found in managing patients on strict chemotherapeutic protocols in busy general medical and paediatric wards with limited isolation facilities. Difficulties were even more pronounced in ensuring regular outpatient follow-up examination and maintenance therapy in patients who did not understand the full implications of the diagnosis and the necessity to continue treatment when feeling clinically well. In adults the importance of maintaining regular employment and income often outweighed the importance of attending hospital regularly. Hospitalization for initial induction, radiation therapy and periodic reinduction was therefore essential and often prolonged, with the attendant high risk of intercurrent infection. This was a particular problem with children, in whom chemotherapy was frequently interrupted or delayed because of intercurrent infections. These children often spent months in hospital and were therefore virtually 'lost' to their families, who might only be able to visit them infrequently. In patients with acute myeloblastic leukaemia in whom complete remission was not achieved but who were rendered aplastic with chemotherapy, prolonged hospitalization was also a problem and severe bacterial infections were the major cause of death.

It is important that specific socio-economic, employment and transportation difficulties of patients in underdeveloped and developing countries be taken into consideration when devising regimens for long-term treatment of patients with neoplastic disease to ensure that medical therapy does not aggravate rather than alleviate the problem. Emphasis should be placed on education so that patients learn to seek medical advice early and persevere with therapy to ensure an optimal outcome. The training of district nurses, health visitors and social workers in the care and support of patients on neoplastic maintenance therapy could then be supervised at home, attendance at follow-up clinics improved and appropriate support provided for the family.

The assistance and co-operation of Dr K. Stevens, Department of Haematology, South African Institute for Medical Research, are gratefully acknowledged.

REFERENCES