CHRONIC MYELOID LEUKAEMIA IN MALAYSIAN CHILDREN

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SYNOPSIS

A 13 year review at the University Hospital, Kuala Lumpur reveals that chronic myeloid leukaemia (CML) constitutes 4.3% of all childhood leukaemia. Adult type of CML occurs in older children and is associated with marked splenomegaly, leukocytosis and thrombocytosis and the presence of Philadelphia chromosome. Although the initial response to busulphan was encouraging most of the patients succumbed; 2 patients underwent acute lymphoblastic transformation. Juvenile CML occurs in younger children and is associated with less marked splenomegaly, leukocytosis and thrombocytopenia and the presence of elevated fetal haemoglobin levels. The disease is characterised by an acute fulminating course. Despite improved survival in acute lymphoblastic leukaemia, the outlook for chronic myeloid leukaemia in childhood remains poor and treatment needs re-evaluation.

INTRODUCTION

Chronic myeloid leukaemia (CML) is uncommon in childhood and accounts for only 2-5% of cases in Caucasian children (1, 2, 3). Two distinct forms have been described, namely - the juvenile and the adult type. Philadelphia (PH^1) chromosome is rarely seen in children; the Manchester Children's Tumor Registry has reported only 9 cases in 23 years (4).

As most of our knowledge of CML has been derived from studies in the developed countries, we review here our experience of CML in childhood, at the Paediatric Department, University Hospital, Kuala Lumpur.

MATERIAL AND METHOD

During the period March 1967 to March 1980, 168 cases of leukaemia were admitted to the Paediatric Unit including 7 cases of CML. The diagnosis was based on observation of proliferation of cells of the granulocytic series at all stages of development in the blood and bone marrow (5). The patients were classified into adult and juvenile CML according to their bone marrow and cytogenetic findings. Ph^1 chromosome, when present, established the diagnosis of adult CML.

All patients received busulphan; the treatment was aimed at stabilising the leucocyte count at 10,000/ul.

RESULTS

Of the 7 cases, 5 were classified as adult CML and 2 as juvenile CML.

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Adult CML

The 5 cases (4 Chinese and 1 Indian) comprised 4 males and 1 female whose mean age was 6.5 years and ranged from 3 to 10 years. The mean duration of symptoms was 4 weeks and the commonest presenting complaint was abdominal distension. Hepatosplenomegaly and generalised lymphadenopathy were found in almost all patients. The mean spleen size was 13 cm and ranged from 8-22 cm. One patient had bilateral fundal infiltration (Table I).

Anemia and marked leucocytosis were present in all cases (Table II). Two patients had thrombocytosis and 4 had increased numbers of circulating nucleated red blood cells and elevated serum B12 levels. Fetal haemoglobin and leucocyte alkaline phosphatase activity were within normal limits except in 1 patient. Ph^1 chromosome was detected in only 1 case.

The details of treatment and outcome are shown in table III. One patient (case 2) with central nervous system involvement also received intrathecal methotrexate and cranial irradiation with good response and is alive and well at 40 months. Case 3 responded poorly to busulphan and was given splenic irradiation followed by 6 mercaptopurine. Despite initial improvement, the disease became refractory and the patient died within 33 months of diagnosis. One patient (case 1) defaulted treatment.

Blastic metamorphosis was observed in 2 children of whom one (case 4) received a course of TRAV followed by vincristine and prednisolone and 3 courses of VAC with poor response and died of pseudomonas septicemia within 4 months. The other (case 5) showed acute myeloblastic transformation 22 months after diagnosis and became pancytopenic after 1 course of TRAV. Bone marrow examination 2 months later revealed lymphoblastic metamorphosis which was treated with vincristine, prednisolone and intrathecal methotrexate. The patient finally succumbed to bronchopneumonia and pseudomonas septicaemia.

Juvenile CML

The 2 patients with juvenile CML (1 Chinese and 1 Indian) included 5 month old male infant and a 3 year old girl with symptoms for 3 weeks and 12 weeks respectively. Both presented with abdominal distension, hepatosplenomegaly and generalised lymphadenopathy. Their spleens measured 2 and 4.5 cm respectively. The older patient had epistaxis and purpura (Table I).

Anemia, leukocytosis and thrombocytopenia were observed in the 2 patients (Table II). Both had elevated serum B12 and fetal haemoglobin levels and nucleated red blood cells in peripheral blood. Leucocyte alkaline phosphatase activity was depressed in 1 patient. One patient was lost to follow up while the other responded poorly to busulphan and 6 mercaptopurine and died within 9 months (Table III).

DISCUSSION

The incidence of CML and the male preponderance noted in our series correlates well with that seen in Caucasian children (1, 6, 2, 3). Adult CML occurs in the older age group and is associated with more marked splenomegaly (7). One valuable parameter in differentiating adult from juvenile CML is the myeloid : erythroid ratio (7). Juvenile CML demonstrates both myeloid and erythroid hyperplasia (M : E ratio 2 : 1 - 5 : 1) while adult CML shows marked myeloid hyper-

Table I: PRESENTING FEATURES OF CHILDREN WITH CML (UHKL 1967 - 1980)

Type of CML	Case No.	Symptoms	Duration (weeks)	Liver (cm)	Spleen (cm)	Lymph-adenopathy	Other signs
Adult	1	abdominal distension	1	5	8	–	–
	2	lethargy weight loss anorexia	8	6.5	12	+	bilateral fundal infiltration
	3	weight loss abdominal distension	2	6	15	+	–
	4	bone pain abdominal distension	5	3	22	+	–
	5	abdominal distension	4	1.5	8	+	–
Juvenile	6	pallor abdominal distension	3	10	2	+	–
	7	epistaxis abdominal distension	12	6	4.5	+	purpura petechiae

Table II: SUMMARY OF HAEMATOLOGICAL FEATURES AT TIME OF DIAGNOSIS IN CHILDREN WITH CML (UHKL 1967 - 1980)

Type of CML	Adult	Juvenile	
	Mean (range)	Case 6	Case 7
Hb gm%	7.0 (4.9 - 10.0)	8.9	9.0
WBC/ul	241,920 (66,400 - 488,800)	164,866	18,700
blasts (%)	5.6 (1 - 12)	10	8
promyelocytes + myelocytes (%)	18.2 (9 - 26)	24	9
metamyelocytes (%)	18.0 (12 - 27)	9	13
neutrophils (%)	45.4 (37 - 58)	41	48
lymphocytes (%)	7.4 (2 - 15)	10	19
monocytes (%)	1.6 (0 - 4)	2	3
platelets 10^3/ul	364 (106 - 660)	106	50
nuc rbc/100 wbc	7 (1 - 19)	3	5
LAP score	74 (29 - 198)	2	68
HbF (%)	1.2 (0.02 - 2.1)	11.2	37.0
Se B12 pg	4298 (857 - 7030)	1429	1651

Table III: TREATMENT AND OUTCOME IN CHILDREN WITH ADULT CML (UHKL 1967 - 1980)

Type of CML	Case No.	Trans-formation	Treatment		Survival (mo)	
			chronic phase	trans-formation phase	from diagnosis	from transformation
Adult	1	—	BU	—	—	—
	2	—	BU IT MTX cran. rad.		36 (still alive)	—
	3	—	BU splenic rad.	—	33 (died of progressive disease)	
	4	lympho-blastic	BU	TRAV VCR + PNL, VAC	5	4 (died of pseud. septicaemia)
	5	myeloblastic lympho-blastic	BU	TRAV VCR + PNL IT MTX	27	5 (died of pseud. septicaemia)
Juvenile	6	—	BU	—	LTFU	—
	7	—	6 MP		(died of haemorrhage)	

BU : busulphan, VCR : vincristine, PNL : prednisolone
TRAV : thioguanine + rubidomycin + cyctosine arabinoside + vincristine
VAC : vincristine + adriamycin + cyclophosphamide
IT MTX : intrathecal methotrexate
LTFU : lost to follow up

plasia (M : E ratio 10 : 1 - 50 : 1). Other useful parameters include the leukocyte and platelet counts. Leukocytosis is more marked in adult than in juvenile CML. Thrombocytosis is characteristic of adult CML while thrombocytopenia is an early feature of juvenile CML.

The fetal haemoglobin (HbF) level, significantly elevated in juvenile CML is probably due to defective B-chain synthesis secondary to the leukemic process (3). Ph' chromosome, positive in one of our patients, is an abnormally small chromosome 22, due to translocation of a portion of its long arm usually onto chromosome 9 (7). When present it establishes the diagnosis of adult CML but may occur in other myeloproliferative disorders like polycythemia (8).

Blastic transformation may complicate CML and is

associated with increased failure of maturation and continued overproduction of immature cells (9), most commonly promyeloblast or myeloblasts and sometimes lymphoblasts mimicking acute myeloid or acute lymphoblastic leukemia. Blast crisis occurs earlier in Ph^1 chromosome negative cases (10). Two of our adult CML patients demonstrated blastic transformation. While 80% of adult CML undergo transformation (11), typical metamorphosis is rarely seen in juvenile CML (7). None of our juvenile CML demonstrated metamorphosis. Various drug combinations have been used when transformation occurs, but the results have been poor (12). Terminal deoxynucleatidyl transferase assay has been used to select cases responsive to vincristine and prednisolone (10).

Busulphan, is probably the best treatment available for CML (14, 13). The question whether maintenance treatment with busulphan should be given has not been settled (8). Splenic irradiation is no longer used alone for treatment of CML. The Medical Research Council (MRC) trial (15) showed the median survival of patients treated with intermittent external irradiation was shorter than that of those treated with oral busulphan. It however remains a practical method of obtaining rapid reduction of spleen size in some cases resistant to busulphan. Other drugs which may be effective are 6 mercaptopurine, cyclophosphamide, hydroxyurea and melphalan (14). Two of our patients received 6 mercaptopurine with poor response.

Intrathecal methotrexate and cranial irradiation have yielded gratifying results in the presence of CNS involvement (10). One of our patients treated similarly is still alive at the end of the study period.

The mean survival of our cases of adult CML is longer than that of juvenile CML, a finding similarly noted by other workers (3, 14, 7). It is difficult to say if treatment has influenced survival. Some workers feel that the median survival is not significantly increased compared to untreated controls. Although many cases may achieve clinical and haematological improvement with simple treatment, the majority will eventually enter a refractory phase (15). The liberal use of blood transfusion and antibiotics and attention to nutrition are probably of greater value in prolonging survival (7).

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