Treatment Outcome Of Children With Acute Lymphoblastic Leukaemia In HUSM

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ABBREVIATIONS

AIEOP	Italian Association of Pediatric Hematology and Oncology
ALL	Acute lymphoblastic leukaemia
AML	Acute myeloblastic leukaemia
BFM	Berlin-Frankfurt-Munster
BM	Bone marrow
BMA	Bone marrow aspirate
CCG	Children's Cancer Group
CCRP	Childhood Cancer Registry of Piedmont
CI	Confidence interval
CLCG	Children Leukemia Cooperative Group
CNS	Central nervous system
CSF	Cerebrospinal fluid
EFS	Event free survival
EORTC	European Organization for Research and Treatment of Cancer
FAB	France American British
HR	Hazard ratio
HUSM	Hospital Universiti Sains Malaysia
IQR	Interquarter range
MRD	Minimal residual disease
RR	Relative risk
SR	Standard risk
TCCSG	Tokyo Children's Cancer Study Group
VHR	Very high risk
WBC	White blood cell

ABSTRAK

Pengenalan

Kanser Leukemia Lymphoblastic Akut adalah kanser yang paling kerap terjadi di kalangan kanak-kanak. Sehingga masa kini, tiada kata sepakat di peringkat kebangsaan mahupun antarabangsa berkenaan pengkelasan risiko serta jenis rawatan kemoterapi yang digunakan. Oleh yang demikian, amat sukar untuk kita membuat perbandingan dari segi keberkesanan rawatan secara keseluruhan. Di Hospital Universiti Sains Malaysia (HUSM), kanak-kanak tersebut di berikan rawatan kemoterapi menggunakan protokol EORTC. Pusat Onkologi lain di Malaysia menggunakan protokol yang berlainan. Hanya satu kajian di lakukan di Malaysia berkenaan keberkesanan rawatan kemoterapi. Kajian ini adalah yang pertama seumpamanya untuk di lakukan untuk menilai hasil rawatan di kalangan kanak-kanak yang mendapat rawatan kemoterapi di HUSM.

Tujuan Kajian

Tujuan utama kajian ini di jalankan adalah untuk menilai pencapaian hasil rawatan penyakit leukemia di kalangan kanak-kanak yang di rawat di Pusat Onkologi HUSM. Tujuan spesifik adalah untuk menentukan kadar survival dan faktor risiko kejadian leukemia berulang dan kadar kematian di kalangan kanak-kanak yang mendapat Leukemia Lymphoblastic Akut yang menggunakan kemoterapi protokol EORTC.

Metodologi

Kajian ini di kendalikan di Pusat Onkologi Kanak-kanak di HUSM. Ia adalah kajian secara retrospektif dan melibatkan kanak–kanak yang di sahkan mendapat kanser Leukemia Lymphoblastic Akut serta mendapat rawatan kemoterapi, bermula dari 1 Januari 1990 sehingga 31 Disember 2003. Kanak–kanak berumur antara 1 hingga 13 tahun serta memenuhi semua criteria yang di tetapkan sahaja termasuk dalam kajian ini.

Keputusan

Seramai 138 kanak-kanak telah di sahkan mengalami Leukemia Lymphoblastic Akut dalam tempoh dari 1 Januari 1990 sehingga 31 Disember 2003 di HUSM. Bagaimanapun, hanya 102 kes sahaja yang memenuhi semua criteria yang telah di tetapkan dan dapat di analisakan. Purata tempoh masa kanak-kanak yang masih dalam susulan adalah 93 bulan. Tempoh masa minimum kanak-kanak yang masih dalam susulan adalah 37 bulan dan tempoh masa maksimun adalah 186 bulan. Kebanyakan Leukemia Lymphoblastic Akut berulang dalam masa 2 tahun selepas di diagnosa. Hanya 2 kejadian Leukemia Lymphoblastic Akut berulang selepas 5 tahun. Kejadian leukemia berulang paling kerap adalah pada tulang sum-sum. Keseluruhan kadar survival pada 1 tahun, 3 tahun dan 5 tahun adalah 81.4% (SE $\pm$ 3.9), 59.8% (SE $\pm$ 4.9) dan 55.3% (SE $\pm$ 5.0).

Analisa 'Multiple Cox proportional hazard model (forward LR)' menunjukkan umur kanak-kanak, tindakbalas awal dengan rawatan prednisolone sahaja serta jumlah sel darah putih adalah faktor risiko kejadian leukemia berulang. Risiko mendapat leukemia berulang atau mati di kalangan kanak-kanak berumaur 10 hingga 13 tahun adalah hampir 4 kali ganda (95% CI 1.47; 10.44, p=0.006); 2.3 kali ganda (95% CI 1.09; 5.00, p=0.030) bagi kanak-kanak yang sel darah putih melebihi 100.0 $X10^3/\mu L$ semasa di diagnosa; dan 2.6 kali ganda (95% CI 1.28; 5.20, p=0.008) bagi kanak-kanak yang tidak bagus bertindakbalas awal dengan rawatan prednisolone sahaja.

Kesimpulan

Kadar survival di kalangan kanak-kanak yang mendapat kanser Leukemia Lymphoblastic Akut adalah setaraf berbanding dengan negara yang sedang membangun, tetapi masih kurang jika di bandingkan dengan negara maju. Kebanyakan Leukemia Lymphoblastic Akut berulang dalam masa 2 tahun selepas di diagnosa terutamanya di sum-sum tulang.

ABSTRACT

Introduction

Acute lymphoblastic leukaemia is the most common malignant disease in children. There is neither national or international consensus about risk assignment, and no uniformed chemotherapy regime accepted. As a result, it is often difficult to compare the outcome from one group with another. In Hospital Universiti Sains Malaysia (HUSM), the children were treated using EORTC protocol. Other centers in Malaysia treat childhood ALL with different treatment protocol. There was only one formal study reported regarding the outcome of children with ALL in Malaysia. However none comparative study of the effectiveness of each treatment protocol carried in Malaysian population. This study was the first to analyse childhood ALL in HUSM.

Objectives

The main objective was to evaluate treatment outcome of children with ALL who received chemotherapy at Pediatric Oncology Unit in HUSM. The specific objective was to determine survival rate and risk factors for relapsed ALL and death among children with ALL treated with EORTC treatment protocol.

Methodology

The study was conducted at Pediatric Oncology Unit in HUSM. This was a retrospective study involving children with ALL who was diagnosed and treated between 1st January 1990 and 31st December 2003. Children aged 1 to 13 years and fulfilled the inclusion and exclusion criteria would be enroll in the study.

Results

There were a total of 138 children with diagnosis of ALL and received treatment at Pediatric Oncology Unit in HUSM from 1stJanuary 1990 to 31st December 2003. A total of 102 children who fulfilled all inclusion and exclusion criteria were available for further review. The mean duration of follow-up was 93 months (SD 40). The minimum follow-up duration was 37 months and maximum duration was 186 months. Most of relapse occurred within 2 year after diagnosis. Only 2 cases of relapse occurred 5 years after diagnosis. Isolated BM relapse (22%) was the most common site of relapse. Overall EFS rate at 1, 3 and 5 years was 81.4% (SE $\pm$ 3.9), 59.8% (SE $\pm$ 4.9) and 55.3% (SE $\pm$ 5.0) respectively.

Multiple Cox proportional analysis showed children aged, WBC count at diagnosis and early response to single prednisolone were the significant prognostic factors for the outcome of children with ALL. There was increased risk of poor outcome (relapse or death) in children aged at 10 to 13 years at about 4 times (95% CI 1.47; 10.44, p=0.006); 2.3 times (95% CI 1.09; 5.00, p=0.030) in children with WBC count at diagnosis more than 100.0 $X10^3/\mu L$; and those poor early response to single prednisolone at about 2.6 times (95% CI 1.28; 5.20, p=0.008).

Conclusion

Survival in this was comparable to developing countries but study remained low compared to developed countries. Most of relapse occurred within 2 year after diagnosis with isolated BM relapse was being the most common site of relapse.

1.0. INTRODUCTION

Hospital Universiti Sains Malaysia (HUSM) was built in 1984. The Paediatric Oncology Unit officially functioned around 1989. HUSM was the tertiary center for East-coast of Peninsular Malaysia, including Kelantan, Terengganu and Pahang. This center caters most of childhood malignancy, mainly from Kelantan and Terengganu. Some children from Pahang preferred to seek treatment at another tertiary hospital nearby. For childhood ALL, they were treated with EORTC protocol. Other centers in Malaysia treat childhood ALL with different treatment protocols. In Malaysian population, only one formal study done regarding the outcome of childhood ALL at Hospital Universiti, Kuala Lumpur (Ng *et al.*, 2000). There was no comparative study regarding the effectiveness of each treatment protocol done in Malaysian population. This study was the first to analyse childhood ALL who received treatment in HUSM.

1.1. Epidemiology

Acute leukaemia is the most common malignant disease in children. The worldwide incidence is 35 cases per million children per year. Acute lymphoblastic leukaemia (ALL) accounts for approximately 80% of childhood leukaemia, another 15 % were acute myelogenous leukaemia, and 5% were chronic leukaemia. The incidence of the disease increased per year. A study conducted in Thailand between 1985 and 2002 reported that the incidence has been increasing by 2.4% per year in boys (95% CI: -0.5 to 5.3) and 4.1% per year in girls (95% CI;1.1 to 7.2) (Kamsa-ard *et al.*, 2006). The increasing incidence could be due to multifactor including environmental pollution in industrialized era.

Most of the studies showed ALL was higher in boys than in girls with a peak incidence between age 1 to 4 years old (Goubin *et al.*, 2006; Pastore *et al.*, 2003). One of the study conducted in France between 1990 and 2000 with 3 995 children involved up to aged of 14 years showed the number of children aged 1 to 4 years was 1925 (48%), whereby the children aged less than 1 year was 121 (3%), aged 5 to 9 years was 1209 (30%) and aged 10 to 14 years was 740 (19%) (Goubin *et al.*, 2006). No clear explanation exists for the predominance of boys. There was a suggestion that a higher susceptibility for infections in boys might play a role in their incidence of ALL (Plasschaert *et al.*, 2004).

1.2. Etiology

ALL is a disease characterized by an uncontrolled proliferation and maturation arrest of lymphoid progenitor cells in the bone marrow resulting in excess of malignant cells. The cause of ALL was unknown. The leukaemic transformation involved complex interactions between host susceptibility, chromosomal damage secondary to physical or chemical exposure, and possibly incorporation of genetic information transmitted virally into susceptible progenitor cells. Pui in review articles mentioned few studies found several inherited genetic abnormalities that predispose to leukemia including Down's syndrome, Fanconi's anemia, Bloom syndrome and ataxia-telangiectasia (Pui, 1995).

The relationship between exposure to the atomic bomb and radiation and the development of ALL still not clear. Previous study had been done, however the evidence still weak (Preston *et al.*, 1994). Few epidemiologic studies failed to correlate any environmental

factors including electromagnetic fields, pesticides and maternal smoking as causative agents for ALL.

Among infectious agents, retroviruses have been implicated in leukaemogenesis in human (Ben-David and Bernstein, 1991). Epstein-Barr virus proved to be associated with mature-B cell ALL.

1.3. Presentation

The clinical manifestations of childhood ALL reflect the effects of dysfunctional haematopoiesis which include anemia, abnormal white cell counts and function, fever and thrombocytopenia and infiltration of the leukaemic cells into the organs causing lymphadenopathy, hepatosplenomegaly, and bone pain.

Patients commonly presented with constitutional symptoms including history of fatigue, malaise, lethargy, weight loss, fever and night sweat. They might have bone pain and joint pain. Rarely they presented with asymmetric arthritis, low back pain, diffuse osteopenia, or lytic bone lesion. Patient may presented with CNS involvement, including cranial neuropathies, which often involved 6^{th} and 7^{th} cranial nerve. Nausea, vomiting, headache or papilloedema occurred as a result of meningeal infiltration and obstruction of cerebrospinal fluid (CSF) outflow, leading to increase intracranial pressure. Painless unilateral testicular mass indicating testicular involvement was found in approximately 2% of boys.

Physical findings often include pallor due to anemia either because of bone marrow infiltration by leukaemic cell or chronic illness. Infiltration by leukaemic cells will produce hepatosplenomegaly and generalized lymphadenopathy. Clinical presentation of spontaneous bleeding related to thrombocytopenia are gingival bleeding, epistaxis, petechiae, echymoses or retinal haemorrhage. Dermal involvement by leukaemia cutis might also be found.

1.4. Diagnosis

Presence of blast cells in the peripheral blood was suggestive of leukaemia, but it was not strong enough to confirm the diagnosis. The diagnosis was confirmed by morphological FAB criteria and cytochemistry analyses when at least 25% lymphoblast present in the bone marrow aspirate. Pui and colleagues concluded that, based on immunophenotyping analyses, a firm diagnosis can be made in 99% of cases (Pui and Evans, 1998).

1.5. Classification

1.5.1. FAB Classification

Leukaemic cells, known as blast cells was classified according to morphology of cells. The best, known classification was the FAB classification. The French-American-British (FAB) working group had previously subdivided ALL into 3 types:

L1: small lymphoblasts with little cytoplasm

L2: large lymphoblasts, more cytoplasm, irregular nuclear membranes and prominent nucleoli

L3: Large lymphoblasts and cytoplasm with present of cytoplasmin vacuolization

The L1 subtype was observed more frequently in children (76% - 89%) compared to adults (31 – 43%) (Kamps *et al.*, 2000). L3 represents lymphoblasts of mature B-cell stage which was more common in older children or adults. This classification had a prognostic value. Early trials suggested that L1 was associated with a good prognosis compared to L2 and L3 (Schrappe *et al.*, 2000).

1.5.2. Immunophenotype classification

ALL can be divided into B-lineage and T-lineage cells. Further subclassfication were according to the recognized steps of normal B-cell and T-cell maturation. Based on the differentiation stages of lymphoid progenitors in normal haematopoiesis, leukaemic cell can be classified into null ALL, pro-B, common pre-B, mature B, early T and T cell ALL (Plasschaert *et al.*, 2004). Some researchers suggested, although several stages can be classified, only B-cell precursor, mature B-cell and T-cell leukaemia have been defined as subgroups with prognostic impact and had therapeutic significance (Pui and Evans, 1998).

Chan in review article mentioned there was approximately 85% of ALL are B-cell lineage. Of these, 2% to 3% are mature B-cell ALL which express surface immunoglobulin and are CD20+. About 20% to 30% are pre-B-cell phenotype with presence of cytoplamic, but not surface immunoglobulin. This represents an intermediate stage of B-cell differentiation. The rest, about 67% to 78% are early pre-B-cell type (B-precursor ALL). They lack immunoglobulin expression. The identification was based on presence of common ALL antigen, CD10 and terminal deoxynucleotidyl transferase, CD19 positivity (Chan, 2002).

About 15% of ALL were derived from T-cell lineage. It reflects the stages of thymic differentiation. Most cases are from the early thymocyte stage. T-cell ALL was commonly found in older children or teenage males with leukocytosis, meningeal involvement and mediastinal lymphadenopathy (Uckun *et al.*, 1996).

1.6. Prognostic factors

Numerous prognostic factors have been identified for paediatric ALL. The risk of relapse ALL mostly dependent on risk factors they have. This risk classification system was used to assign treatment, in which children may received intensive or less intensive chemotherapy. Despite on intensive treatment in the high risk group, the rate of relapsed still high (Tsuchida *et al.*, 2000). Various groups and institutions have applied prognostic factors differently to define risk categories. This variability in risk assessment and treatment assignment has made it difficult to evaluate and compare the results from clinical trials conducted by different investigators. Three risk categories was suggested; low risk, moderate risk and high risk (Pui and Evans, 1998).

1.6.1 Gender

A better prognosis for girls than boys has been reported in many literature but this significant difference was not always observed. However, recent epidemiological studies show that gender accounts for only minor significant prognostic value. The difference between genders was not apparent shortly after diagnosis. A small difference appeared after approximately 1 to 2 years and this became statistically significant after 10 years (Pastore *et al.*, 2003). Pastore and colleague conduct the study in Italy from 1979 to 1998

with sample size of 498 showed survival rate at 3 years was 78.6% (SE $\pm$ 2.5) for boys and 82.0% (SE $\pm$ 2.6) for girls. At 5 years, the survival rate in boys was 67.3% (SE $\pm$ 3.0) and 75.0% (SE $\pm$ 3.0) in girls.

The difference was partially explained by the differences in distributions of biological features of leukaemia and mechanisms of reaction to treatment including enzyme deficiency in metabolism of chemotherapy drugs related to sex inheritance. Pui et al reported that boys tend to have T-cell ALL and poor early response. They collected a large sample size of 2,055 between 1962 and 1994 showed 20.9% of boys had T-cell immunophenotype and only 1.7% of girls had T-cell immunophenotype (Pui *et al.*, 1999).

It has been suggested that the testes function as "sanctuary site" with the blood-testes barrier protecting leukaemic cells from anti-cancer drugs. Subsequently, dissemination to the bone marrow resulting in relapse. This theory was not always true. In MRC UKALL VI and VII, a clinical study was done to investigate the effect of testicular irradiation. The randomization study in which, the boys were receive early testicular irradiation or not. The results showed there was a decreased in testicular relapse in the testicular irradiated group, but no reduction in bone marrow relapse (Chessells *et al.*, 1995).

1.6.2. Age

Patient's age at diagnosis was one of the prognostic factors that was easy to determine and had a powerful prognostic significance for B-cell precursor ALL. A poorer prognosis for infants and adolescents had been confirmed in many studies (Smith *et al.*, 1996). A study

showed prognosis for infants with ALL aged less than one year was consistently inferior compared to children aged 1to 9 years, with a 5 year survival rate of 48% (39 – 57).

Children aged 1 to 4 years was the most common age group at presentation and had the best prognosis, with EFS at 5 year of 87% (85 – 88), compared to children aged 5 to 9 years and 10 to 14 years with a 5 years EFS of 83% (81 – 85) and 72% (69 -76) respectively (Goubin *et al.*, 2006). The study conducted by Goubin and colleague in France between 1990 and 2000 with large sample size of 3960. Another study conducted by Pastore and colleague between 1979 and 1998 with sample size of 498 showed EFS at 5 years of 79.1% (SE±2.7) for children aged 1 to 4 years; 70.9%(SE±3.7) for children aged 5 to 9 years; and 68.5%(SE±5.0) for children aged 10 to 14 years (Pastore *et al.*, 2003).

1.6.3. Initial WBC Count

The initial WBC count at diagnosis was a representative of tumour burden. Some researcher found that it was a reflection of the biological behaviour of ALL cells (Plasschaert *et al.*, 2004, Smith *et al.*, 1996). Most of the studies showed that WBC count at presentation was less than 50 $X10^3/\mu L$, about 40 to 80% of children (Schrappe *et al.*, 2000, Vilmer *et al.*, 2000, Tsuchida *et al.*, 2000). Few children presented with WBC count more than 100 $X10^3/\mu L$, about 10% (Sackmann-Muriel *et al.*, 1999). A local study with sample size of 575 children between 1st January 1980 and 30th May 1995 (Ng *et al.*, 2000)., published in 2000 showed 78% of children presented with WBC count was less than 50 $X10^3/\mu L$ and 22% of children presented with WBC count more than 50 $X10^3/\mu L$ (Ng *et al.*, 2000).

Smith and colleagues had proposed regarding risk classification, in which a WBC count more than 50 $X10^3/\mu L$ was considered high-risk patient, regardless of gender and age at presentation (Smith *et al.*, 1996). Another multi center study conducted in Japan, from 1992 to 1995 with sample size of 347 showed EFS at 5 year in children with WBC count less than 10 $X10^3/\mu L$ was 66.5% (SE $\pm$3.8), 64.2% (SE $\pm$4.7) for children with WBC count 10 to 49 $X10^3/\mu L$, 65.3% (SE $\pm$10.6) for children with WBC count 50 to 99 $X10^3/\mu L$ and 50.5% (SE $\pm$8.0) for children with WBC count more than 100 $X10^3/\mu L$ (Tsuchida *et al.*, 2000).

1.6.4. Hepatosplenomegaly and lymphadenopathy

Multiple organs such as liver, spleen and lymph nodes were susceptible to infiltration by leukaemic cells. Nodal enlargement was an indirect measured of tumour burden and was associated with poor prognosis. Children with mediastinal lymph node enlargement had poor prognosis. They usually carried T-cell ALL and were related to thymus enlargement.

Liver and spleen enlargement of 5cm below the costal margin were noted to had poor prognosis (Plasschaert *et al.*, 2004). About 34% of children with ALL had liver palpable of more than 5cm below subcostal margin at presentation (Ng *et al.*, 2000). The similar study also found there was 26% children had spleen palpable of more than 5cm below subcostal margin at presentation.

In multi center study conducted in the United States and Canada, with a large sample size of 8,447 children, treated with Children's Cancer Group (CCG) therapeutic protocol from 1983 to 1995. They reported that children with enlarged spleen had a relative risk (RR) of