Original Artcle

Liver dysfunction in children with hematologic malignancy or solid tumor

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ABSTRACT

Background Deficiencies in liver synthetic function can only be detected if the damage is severe, which are more often due to non hepatic factors such as malignancies, both hematologic and solid tumor.

Objective To assess liver function in children with either hematologic malignancy or solid tumor and to find out which one of them mostly affects liver function.

Methods A retrospective study was conducted on 125 children with malignancies in the Sub division of Hemato-Oncology Department of Child Health, Adam Malik Hospital, Medan, from January 1999 until May 2000. The inclusion criteria included all patients who were younger than 15 years and had not received any treatment yet. The differences between prevalent liver dysfunction in both groups were assessed by using chi-square test; Fisher's exact test was used to know the type of liver cell damage.

Results Liver dysfunction occurred in both types of malignancies. A decrease of albumin level was not significant in both groups. There was a statistically significant difference between the prolonged prothrombine time (PT) in hematologic malignancy (26.4%) and that in solid tumor (10.4%) with p=0.03. There was no significant difference in the elevation of serum transaminase concentration, total bilirubin, and alkaline phosphatase. Based on aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ratio, we found that the type of liver cell damages was infiltrative disorders, occurred 13 out of 20 cases with elevated AST and ALT.

Conclusion Liver dysfunction occurred in both types of malignancy; it occurred more frequently in hematologic malignancy than in solid tumors **[Paediatr Indones 2003;43:126-131].**

Keywords: liver dysfunction, hematologic malignancy, solid tumor, children.

L iver has a very large functional reserve. Deficiencies in synthetic function can only be detected if the damage is severe; such abnormalities are more often due to non hepatic factors.[1,2] Malignancy is one of them, hematologic malignancy as well as solid tumors. [1-4] Hepatomegaly, icterus, and asymptomatic abnormalities frequently occur in patients with lymphoma, leukemia and neuroblastoma.[5] Acute lymphoblastic leukemia (ALL) may present with hepatomegaly (about 68%),[6] and elevated transaminase (100–400 IU/l).[4] Hepatic involvement is observed in 25% to nearly 50% of patients with Non Hodgkin's lymphoma, and associated with abnormal biochemical test.[5] In neuroblastoma, massive involvement of the liver may occur especially in infant with widespread disease.[7,8] Besides that, liver dysfunction can also be caused by chemotherapy agents, the most common are methotrexate (MTX), 6-mercaptopurin, and l-asparaginase. The severity of liver damage could be related to both high dose and long-term duration of treatment.[9,10-12] Elevated transaminase enzyme is indicated to dose reduction.[9,10] The occurrence of clinical or biological liver disturbances in patients treated with antineoplastic agents has become a challenging diagnosis and management problem.[10] Assessment of liver function

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is necessary to determine the staging of the disease and to establish the treatment plan.[5] To our knowledge, there is no simple reported data about liver function in children with malignancy in Indonesia.

The purpose of this study was to assess liver function in children with malignancy, either hematologic malignancy or solid tumors, and to find out which one of them influences it more.

Methods

A retrospective study was conducted in all patients who were admitted in the Sub division Hemato-Oncology Department of Child Health , Adam Malik Hospital from January 1, 1999 to May 31, 2000. The inclusion criteria were all patients younger than 15 years old, had malignancy disease, and had not received any treatment yet, such as chemotherapy, radiotherapy or surgery. We excluded patients with hepatic malignancy. Data obtained from medical records included age, sex, nutritional state, serum albumin concentration, prothrombine time (PT), total bilirubin, transaminase enzymes, i.e., aspartate amino transaminase (AST), alanine aminotransaminase (ALT) and alkaline phosphatase (ALP).

The term "liver function test" includes true test of hepatic function, (e.g., albumin, PT), excretory function (e.g., bilirubin), and test of reflective hepatic in-flammatory activity (e.g., serum transaminase). Liver dysfunction was defined by a decrease of albumin level, prolonged PT, elevation of transaminase or alkaline phosphatase.[1,2,13]

The nutritional state was classified according to National Center for Health and Statistics WHO (NCHS-WHO),[14] and Semiloka Antropometri Indonesia, 1991.[15] Hypoalbuminemia was defined as serum albumin level less than 3.9 g/dl for age <5 years, and below 4 g/dl for age 4-19 years. Prolonged PT was defined as a prolongation of 2 seconds from normal/control PT.

Hyperbilirubinemia was defined as serum bilirubin >1 mg/dl. Elevated AST if AST>55 u/l for age of 1-9 years, and >45 u/l for age of 10-14 years. Elevated ALT if ALT>45 u/l. Elevated ALP if ALP>420 u/l for age >9 years and >560 u/l for age of 10-19 years.[16] Laboratory assessment were performed in the Pathology Clinic Department, Adam Malik Hospital. Level of albumin, AST and ALT were assessed by using Autometric Selectra 2. Value of bilirubin and ALP were assessed by using Spectronic 401, while PT was assessed by using Co ag-A-Mate MTX from Organon Technica.

The differences between prevalent liver dysfunctions were assessed by using chi-square; Fisher's exact test was used to determine the type of the liver cells damage. The statistical significant was accepted with confident level of 95% (p<0.05).

TABLE 1. CHARACTERISTICS OF PATIENTS

Characteristic	Hematologic malignancy		Solid tumor		p
	n	%	n	%	
Total	74	59.2	51	40.8	
Age					0.014 *
< 2 years	10	8	16	12	
2 – 4 years	21	16	19	15	
5 – 9 years	21	16	10	8	
≥ 10 years	22	17	6	4	
Sex					0.008 *
girl	23	18	28	22	
boy	51	40	23	18	
Nutritional state (BW/A)					0.005*
good nutrition	5	4	11	8	
fair nutrition	30	24	8	6	
poor nutrition	27	21	17	13	
bad nutrition	12	9	15	12	
Nutritional state (BL/A)					0.377
good nutrition	20	16	21	16	
fair nutrition	29	23	15	12	
poor nutrition	17	13	9	7	
bad nutrition	8	6	6	4	

TABLE 2. DISTRIBUTION OF MALIGNANCY

Type of malignancy	n	%
Hematologic		
Acute Lymphoblastic Leukemia (ALL)	38	30.4
Non-Hodgkins Lymphoma (NHL)	16	12.8
Acute Non Lymphoblastic Leukemia (ANLL)	7	5.6
Acute Myeloblastic Leukemia (AML)	6	4.8
Chronic Myelositic Leukemia (CML)	4	3.2
Hystiocitosis	2	1.6
Multiple myeloma	1	0.8
Solid tumor		
Retinoblastoma	16	12.8
Neuroblastoma	6	4.8
Willm's tumor	6	4.8
Embryonal carcinoma	4	3.2
Rhabdomyosarcoma	4	3.2
Nasopharyngeal carcinoma	3	2.4
Teratoma	3	2.4
Other *	9	7.2
Total	125	100.0

* fibrosarcoma, liposarcoma, mesotelioma, myxoma peritonii, neurofibroma, genitourinarius, extracranial tumor, lung tumor, squamous cell carcinoma

Results

There were 157 patients of malignancy recorded in Adam Malik Hospital Medan from January 1, 1999 to May 31, 2000. We excluded 32 children in which 29 did not have complete laboratory assessment and 3 suffered from hepatic malignancy. The remaining 125 children consisting of 74 (59.2%) of hematologic malignancies and 51 (40.8%) solid tumors were analyzed in this study.

Table 1 shows the characteristics of patients, where distribution of age, sex, and nutritional state (bodyweight by age) were significantly different between hematologic malignancy and solid tumors (p=0.014, 0.08, and 0.05 respectively).

Table 2 shows that the most common type of hematologic malignancies were acute lymphoblastic leukemia, 38 subjects (30.4%), followed by non-Hodgkin's lymphoma, 16 subjects (12.8%); retinoblastoma was the most common solid tumor, 16 cases (12.8%).

Liver dysfunctions are described in Table 3. Decreased albumin level and prolonged PT were seen in all malignancies. There was a significant difference in prolonged PT, whereas in hematologic malignancy was higher than that of solid tumor (p=0.03), but not in albumin level. Elevated transaminase, bilirubin and alkaline phosphatase were found in only few subjects, and there were no significant differences.

In this study we found only 20 subjects suffered from elevated AST and ALT. The transaminase enzymes ratio is shown in Table 4.

Table 5 shows decreased albumin value that was seen in all nutritional state, especially in fair nutritional and poor malnutritional state (17.6% and 25.6%, respectively)

Discussion

In this study we found that the peak incidence of hematologic malignancy and solid tumor coincides with other authors. Peak incidence of hematologic malignancy was similar at the age of 2-4 years and 5-10 years. While in solid tumors, there was a similarity between boys and girls. Girlchrist [17] reported that the peak incidence of acute lymphoblastic leukemia was found in children between 2-4 years old, while Christ et al[18] reported at the age of 4. In solid tumors, we found the peak incidence at the age of 2-5, in accordance with that found by Christ et al whereas the peak incidence of Willms' tumor was at 2-4 years, neuroblastoma at the first 5 years, and retinoblastoma before 3 years old.[18] Hematologic malignancy occurred more frequently in boys (40.8%) than that

TABLE 3. DISTRIBUTION OF LIVER DYSFUNCTION

Liver function	Hematologic malignancy		Solid tumor		p
	n	%	n	%	
Albumin					
normal	22	17	20	16	0.270
abnormal	52	41	31	24	
PT(prothrombine time)					
normal	41	32	38	30	0.030 *
abnormal	33	26	13	10	
Bilirubin					
normal	56	44	35	28	0.384
abnormal	18	14	16	12	
AST					
normal	51	40	29	23	0.168
abnormal	23	18	22	17	
ALT					
normal	62	49	38	30	0.203
abnormal	12	9	13	10	

TABLE 4. TRANSAMINASE ENZYME RATIO

AST: ALT ratio	Hematologic malignancy	Solid tumor	Total	p
	n	n	n	
> 1	6	7	13	0.642
< 1	2	5	7	
Total	8	12	20	

in girls (18.4%), similar to that found by Christ *et al* [18] and Niemeyer *et al*.[19]

Weight loss is one of the symptom of malignant disease.[20,21] Kibirige *et al*[22] reported that malnutrition is a problem in children with malignancy, while Rickard *et al*[23] suggested that a weight loss equal or greater than 5% was bad. They also reported that if weight loss was below the 5th percentile and height was greater the 5th percentile, then the child was at risk of malnutrition. Weight loss may be due to anorexia, malabsorption, excessive energy loss, ineffective metabolic activity, chemotherapy and psychosocial factors. The most common nutritional state by bodyweight and age were fair nutritional state in hematologic malignancy (24.4%) and poor nutritional state in solid tumors (13.6%) with p=0.030. We can not explain this condition because we did not know the patients' previous bodyweight. This may be due to the inherent factors of the disease or other factors. Nutritional state by body length and age was relatively good in both groups, and there was no significant difference. This finding indicated that nutritional disorders occurred acutely. This condition

may be due to the progress of the disease, which can develop to cachexia.[24]

Measurement of serum albumin is useful in evaluating the patient with parenchymal disease. A decrease in serum albumin level is a sign of hepatic compensation.[11] In this study liver dysfunction was found in both groups, proven by decreased albumin level and prolonged prothrombine time (PT). Decreased albumin level was not significantly different, in contrast to prolonged PT. The prolonged PT was greater in hematologic malignancies (26.4%) than in the solid tumors (10.4%) with p=0.030. PT may be a good indicator for prognosis and become a more specific indicator of impaired synthetic capacity than albumin level.[2] Haskel *et al* reported that deficiency of clotting factors occurred in 16 of 20 patients, and liver dysfunction in 33 of 35 patients. [25]

A decrease of albumin occurred not only in malnutrition patients (40.8%), but also in a good nutrition ones (25.6%). These data indicated that a decrease of albumin was due to the disease, and not due to malnutrition. Kibirige *et al* reported that median weight:height ratio and serum albumin level may be a useful measurement in children with newly diagnosed leukemia to indicate which children that need supplementary nutrition.[22]

Liver cells damage that caused by malignant cells infiltration occurred only in few subjects (9.6%-18.4%), proven by the elevation of total bilirubin, transaminase and alkaline phosphatase, which was not significantly different between the groups. Menard reported that icterus occurred in about 42% of patients who had received 6–mercaptopurine treatment.[10]

TABLE 5. ALBUMIN LEVEL BY NUTRITIONAL STATE BASE ON BODYWEIGHT AND AGE

Albumine	Nutritional state				Total	p
	good nutrition	fair nutrition	poor nutrition	bad nutrition		
	n (%)	n (%)	n (%)	n (%)	n (%)	
Normal	6 (4.8)	16 (12.8)	12 (9.6)	8 (6.4)	42 (33.6)	0.648
abnormal	10 (8.0)	22 (17.6)	32 (25.6)	19 (15.2)	83 (63.4)	
Total	16 (12.7)	38 (30.4)	44 (35.2)	27 (21.6)	125 (100.0)	

Most liver cell damage was infiltration type. It was based on the evidence that AST:ALT ratio of >1 was more frequently found than that of <1 (13/20 vs. 7/20). Liver damage was found in 6 out of 8 patients with hematologic malignancy and 7 out of 12 patients with solid tumors. The difference was not significant (Table 4). It is important to remember that significant liver damage may be present despite these normal levels, such as in patients with cirrhosis and post necrotic inflammatory disorders.[2,10,13] In this study no one suffered from elevated ALP 2x normal, it means no one suffered from cholestasis.

Hepatotoxicity is an important complication of chemotherapy.[10,14] Dahl *et al*[26] reported that the severity of liver damage could be related to both duration and mode of administration of methrotrexate. Goodell *et al*[27] observed evidence of hepatic dysfunction in 22 out of 49 patients who received cytocine arabinoside.

We concluded that liver dysfunction occurs in hematologic malignancy as well as in solid tumors before treatment, indicated by prolonged PT and is more frequently found in hematologic malignancy that in solid tumors.

Based on the data above, it is necessary to perform liver function tests before giving chemotherapy. The dose of chemotherapy should be modified according to the liver function. Once chemotherapy is begun, periodical evaluation of liver function must be performed. The frequency of this evaluation should be modulated according to the hepatotoxic risk of the agent.

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