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THE PRESENT STATUS OF CHILDHOOD CANCER THERAPY IN KOREA*

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Abstract. We have studied the incidence pattern of childhood cancers in Korea. Although the incidence of many tumors in Korea is similar to that in other countries, the incidence of acute myelogenous leukemia, non-Hodgkin's lymphoma and hepatoma is greater in Korean children. Yonsei Cancer Center commenced a study of multimodality treatment of childhood cancers in July 1974. The most striking improvement of survival rate was seen in patients with acute lymphocytic leukemia (50 % at 5 years), Wilms' tumor (65 % at 5 years), neuroblastoma (45 % at 2 years), osteogenic sarcoma (55 % at 2 years) and malignant histiocytosis (20 % at 5 years). This study is an attempt to create a basic framework providing the best possible treatment of childhood cancer in Korea. The data obtained in Korea are briefly compared with those in Japan and the United States.

Key words : childhood cancer, multimodality treatment, survival rate.

With the control of infectious diseases through advances in medicine, we are seeing many changes in the pediatric disease pattern. In particular, cancer has become an important cause of death of children. For instance, in developed countries such as Japan or the U.S.A., cancer is the second leading cause of death in the 1 to 15 year old age group (1, 2). The annual incidence of cancer in the U.S.A. was 12.45 per 100,000 persons under 15 years of age in 1975 (1). According to the Ministry of Health and Welfare of Japan, the annual incidence of cancer was 8.85 in Aichi Prefecture (in 1973) and 12.85 in Kanagawa Prefecture (in 1971) per 100,000 children under 15 years of age (2, 3). In Korea, there has been no study of the incidence of malignant tumors in the pediatric age group. However, if we look at the hospital statistics, 1.7 % of all hospitalized pediatric patients were admitted due to malignant tumor, which has become an important cause of death (4).

There has been considerable improvement in the research and therapy of malignant tumors in developed countries. Ever since Farber (5) reported in 1948 that remission of acute leukemia could be induced with aminopterin, there has been progressive improvement in the cure rate. The Children's Cancer Association of

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Japan was established 15 years ago to concentrate on the research and therapy of pediatric malignant tumors. In addition, the policy that the government is responsible for all expenses incurred in the treatment of pediatric malignant tumor patients undoubtedly contributed to the advance of therapy and the improvement of survival rate. In Korea, cancer research and therapy have received low priority because of the high mortality rate from infectious diseases or pulmonary tuberculosis which was experienced until recently. With economic development and an improved health care system, much more pediatric cancer is being diagnosed and treated than before. Therefore, the need for further research and improved therapy of pediatric cancer is an urgent matter. In 1974, the Yonsei Cancer Center at the Yonsei University Medical College created the Division of Pediatric Oncology to meet this need.

This paper presents the results of our research and therapy in our pioneer study of childhood cancer in Korea utilizing the newly developed multimodality approach. This study analyzes the results of therapy and feasible therapeutic protocols of various pediatric cancers.

METHODS AND RESULTS

The types and incidence of cancer in children. It has been postulated that the occurrence of cancer is different in Korea from the U.S.A., but similar to Japan.

The most common pediatric cancer in Korea is leukemia (59 %), being higher than in Japan (42 %) and the U.S.A. (32.8 %). More significantly, acute myelogenous leukemia consists of 30 % of all pediatric leukemia; this is in marked contrast to the figure in the U.S.A. (15 %) (6), but similar to that in Japan (40 %) (3).

Malignant lymphomas comprise 8.5 % of childhood cancer in Korea (4). This incidence is similar to that in Japan (7.5 %) (2) and the U.S.A. (10.6 %) (7). However, 85 % of childhood lymphoma are non-Hodgkin's lymphoma in Korea. This is higher than in the U.S.A. (60 %), but similar to in Japan (87 %). Ninety percent of non-Hodgkin's lymphoma was classified as diffuse lymphoma. There are substantial data from various studies indicating that about 91 % of non-Hodgkin's lymphoma have an unfavorable histology in Korea. This is similar to the data in Japan, but significantly different from that in the U.S.A. (8, 9).

The incidence of hepatoma comprises 6 % of all pediatric cancers. This is significantly higher than in Japan (2.5 %) and much higher than in the U.S.A. (1.9 %). This phenomenon is probably related to the high incidence of hepatitis-B virus-carriers in Korea. In particular, liver cirrhosis in children due to intrauterine hepatitis-B virus infection probably contributes to the increasing trend of juvenile hepatoma at around the age of ten.

Survival rate of children with acute lymphocytic leukemia. Acute leukemia is the most common malignant disease in children. During the past two decades the prognosis for acute lymphocytic leukemia (ALL) has improved dramatically. With

TABLE 1. CHARACTERISTICS OF 48 CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA

Characteristics	Percent	Characteristics	Percent
Age (year)		Blast (%)	
< 2	8	>95	6
2- 5	52	85-94	23
6-10	34	65-84	40
⩾11	6	<65	31
Sex (male)	62	Platelet ($\times 10^4$/ul)	
WBC ($\times 10^3$/ul)		>100	16
<10	53	20-99	34
10-50	33	<20	50
>50	14	Hepatomegaly	63
Hemoglobin (g/dl)		Splenomegaly	50
< 7	52	Lymphadenopathy	35
7-11	44	Hemorrhage	46
>11	4	Bone pain	20
		Mediastinal mass	6

combination chemotherapy and preventive treatment of the central nervous system (CNS), long lasting, complete remission of ALL is obtainable in children.

We have studied the survival rate of 48 cases of children with ALL from January 1975 to July 1981. Age, sex and symptoms in this group showed no major difference from those of Japan or the U.S.A. There were also similarities in the factors influencing the response to treatment such as high WBC count and organomegaly (Table 1).

The protocol for treatment of ALL in Korea is based on the simplest, most effective and least costly guideline. Complex therapeutic methods to increase the cure rate as used in developed countries is impossible or impractical to put into effect in Korea in many instances. Since most of the patients at Yonsei Cancer Center are referred from all around the country, active cooperation with general pediatricians, *i.e.*, not pediatric oncologists, is required for effective therapy. Therefore, it is most important to have a relatively simple therapy guideline.

In the first phase of treatment, remission is induced by vincristine and prednisolone. Adriamycin or asparaginase may be added to the above combination for high risk patients. The second phase consists of CNS prophylaxis, *i.e.*, 2,400 rads of radiotherapy with intrathecal administration of methotrexate. The third phase is continuation chemotherapy, *i.e.*, the combination of methotrexate and 6-mercaptopurine for up to three years (Table 2).

Complete remission was attained with initial therapy in 43 of the 48 children (90 %). The addition of adriamycin or asparaginase has improved the induction of remission in high risk patients. In this study, CNS leukemia terminated complete remission in 10 patients (20 %). The prescribed drug dosages for continuing

TABLE 2. THERAPEUTIC PROTOCOL FOR ACUTE LYMPHOCYTIC LEUKEMIA

Remission induction (4-8 weeks)	
Vincristine	1.5 mg/m²/week
Prednisolone	40 mg/m²/day
For high risk patients	
Adriamycin	30-40 mg/m²/week
L-asparaginase	10,000 U/m²/day for 10 days
Continuation therapy	
6-mercaptopurine	75 mg/m²/day
Methotrexate	20 mg/m²/week
Central nervous system therapy	
Cobalt 60 therapy, 2400 rads to cranium	
Methotrexate	12 mg/m², intrathecally twice a week for 5 doses

remission were adjusted to the maximum tolerated by patients. The principle guide for dosage adjustment was maintenance of the leukocyte count between 2,500 and 3,500/μl. In some patients, drugs were discontinued because of severe toxicity, fever or infection. The combination therapy may be very toxic to various organs. The most serious clinical problem was infection due to leukopenia and immunosuppression. Therefore, as a principle of management, we required weekly follow-ups at the Pediatric Tumor Clinic to adjust the drug dosage in order to prevent toxicity.

The median duration of survival was 4 years. More importantly, however, 7 children (16.8 %) have been in complete remission for 4 to 8 years and off all the therapy for 1 to 5 years. The failures of therapy were caused by truly resistant leukemia (25 %), fatal infection (20 %) usually by staphylococcal septicemia, CNS relapse (10 %), and bone marrow relapse (45 %). However, this study demonstrated that a significant cure rate is possible in Korea even with a relatively simple treatment protocol. According to the life-table method, the 5-year survival rate was estimated to be about 50 % (Fig. 1) (10).

Survival rate of children with Wilms' tumor. The incidence of Wilms' tumor, the most common intra-abdominal tumor, is about 4 % of all childhood tumors, which is comparable to the figures in Japan and the U.S.A. (1, 3, 6). Wilms' tumor is a childhood cancer in which major and basic therapeutic advances have been established (11, 12).

We treated 34 cases. The clinical symptoms, age and sex ratio of these cases did not differ from those of other countries (Table 3). However, the time between onset and diagnosis was much longer than in developed countries mainly due to inadequate education about early diagnosis and the burden of medical expense. Moreover, 26 % of patients visited hospitals 1 to 6 months after onset. Patients with metastasis at the time of diagnosis consisted of 26.5%. Three major treatment

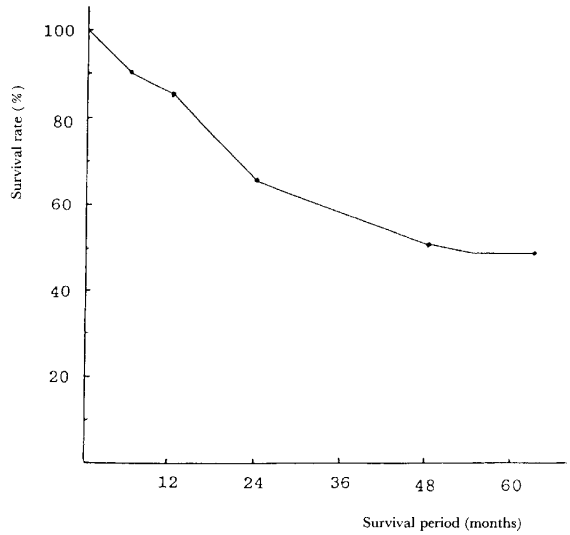


Fig. 1. Survival rate of acute lymphocytic leukemia patients.

TABLE 3. CHARACTERISTICS OF 34 CHILDREN WITH WILMS' TUMOR

Characteristics	Percent	Characteristics	Percent
Age (year)		Stage	
<1	11	I	32
1-2	24	II	27
2-5	46	III	18
>5	19	IV	27
Sex (male)	53	Initial symptoms	
Congenital anomaly	2.9	abdominal mass	85
Pathology (favorable)	90	hematuria	41
Bilateral Wilms' tumor	0	abdominal pain	24
Site (right)	56	fever	24
		hypertension	15

TABLE 4. THERAPEUTIC PROTOCOL (AJUVANT) FOR WILMS' TUMOR

Stage I	
Favorable histology	AMD + VCR
Unfavorable histology	XRT + AMD + VCR
Stages II, III and IV	
Favorable and unfavorable histologies	XRT + AMD + VCR

AMD (Actinomycin D)	15 μg/kg for 5 days, every 8 weeks to 1½ years
VCR (Vincristine)	1.5 mg/m² weekly for 12 weeks
XRT (radiotherapy)	2,500-3,200 rads

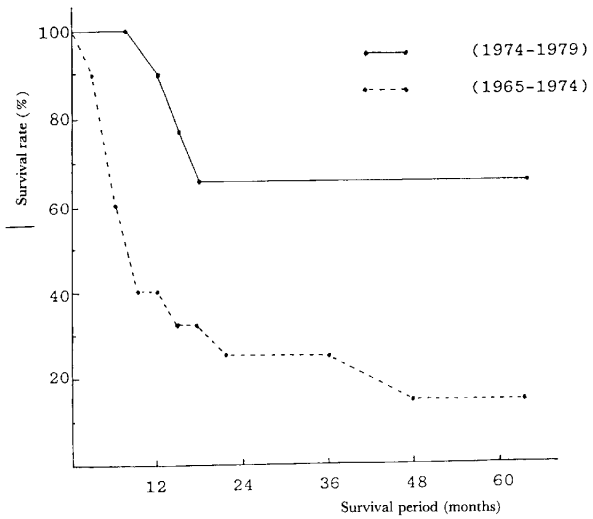


Fig. 2. Survival rate of Wilms' tumor patients with multimodality treatment.

modalities, *i.e.*, surgery, radiotherapy and chemotherapy, were employed. Surgery should be performed as soon as possible following initial evaluation. Radiotherapy was usually begun shortly after surgery. Radiotherapy was recommended for the patients in stage I with unfavorable histology, and those in stages II, III and IV with either histology. In stage I cases with favorable histology, only chemotherapy was recommended without radiotherapy. Combination chemotherapy was administered to all patients with caution, *i.e.*, with daily hematologic evaluation (Table 4).

According to the life-table method, the 5-year survival rate was 64.9 % of the patients who had multimodality treatment (Fig. 2). A good survival rate in stage I and stage II was obtained, *i.e.*, 90 % and 80 %, respectively. Prior to 1974, only 15 % of patients survived 5 years in contrast to 65 % of those treated more comprehensively after 1975 (13). A patient with lung metastasis showed complete recovery after receiving multimodality treatment.

Survival rate of children with neuroblastoma. Neuroblastoma is one of the most common childhood tumors, after leukemia, lymphoma and brain tumor, and followed by Wilms' tumor and soft tissue sarcoma. It accounts for 6 % of all childhood malignancies in Korea (4). The results of treatment have been disappointing; the survival rate of patients with neuroblastoma has not been improved as seen in other childhood tumors following the advances of multimodality therapy.

The favorable factors in the treatment of 33 cases of neuroblastoma from September 1974 to September 1980 were evaluated (14). The sex ratio was 1.2 : 1 showing a slightly higher incidence in males, but sex did not influence survival.

One third of cases occurred in children less than 2 years of age, and all cases were encountered during the first 5 years of life. The survival rate of cases under

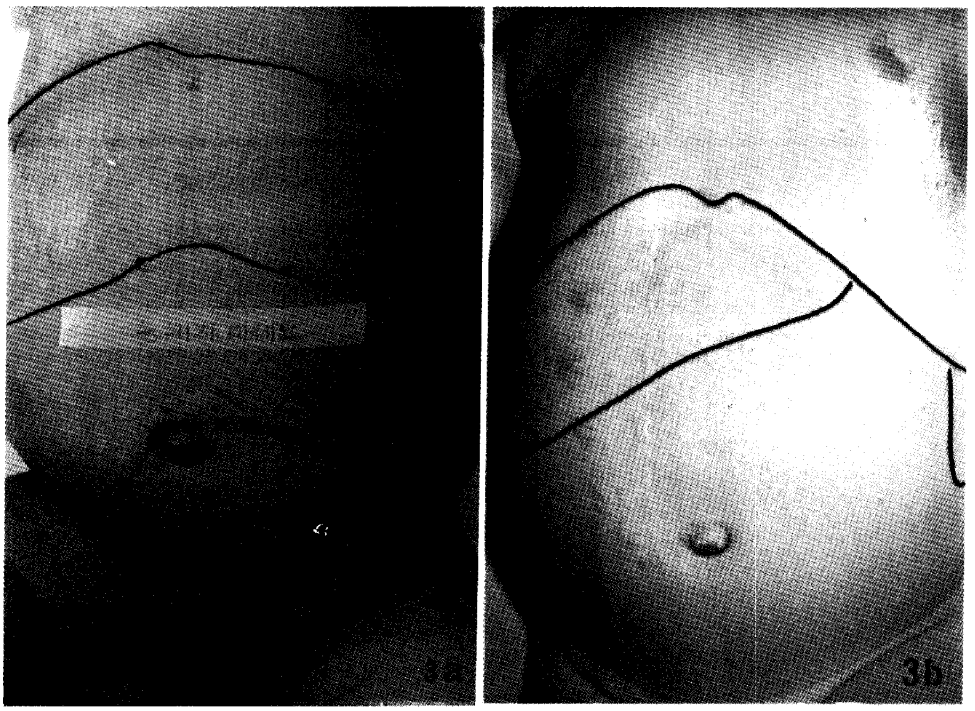


Fig. 3. (a) A three-month-old male with massive involvement of liver by neuroblastoma. (b) Spontaneous regression of the liver occurred following *Klebsiella* septicemia.

1 year of age was 100 %, and that of cases diagnosed between 12 and 24 months was 33 %, whereas that for cases diagnosed beyond the age of 2 was only 9 %. Therefore, the survival rate in neuroblastoma correlated inversely with the age at the time of diagnosis.

Comparison by stage of disease shows only one death among five cases with stage I. In stage IV, 5 % of patients survived for 2 years following diagnosis. One of two stage IV patients resulted in remission after *Klebsiella* septicemia (Fig. 3-a, b). The boy is now four years old and healthy. Children with the primary tumor in the mediastinum or pelvis have a more favorable prognosis than those with intra-abdominal tumors. The survival rate for mediastinal neuroblastoma was 50 %. Patients with ganglioneuroblastoma had a good prognosis and the survival rate was 100 % in this study.

According to the life-table method, the overall two-year survival rate was 45 % (Fig. 4). This depends on the factors discussed above, age being the most important factor and surgery being the most effective therapy.

Survival rate of children with osteogenic sarcoma. Although rare in childhood, osteogenic sarcoma has received attention because of the rapid advances in multimodality treatment, which have resulted in prolonged disease-free survival in a ma-

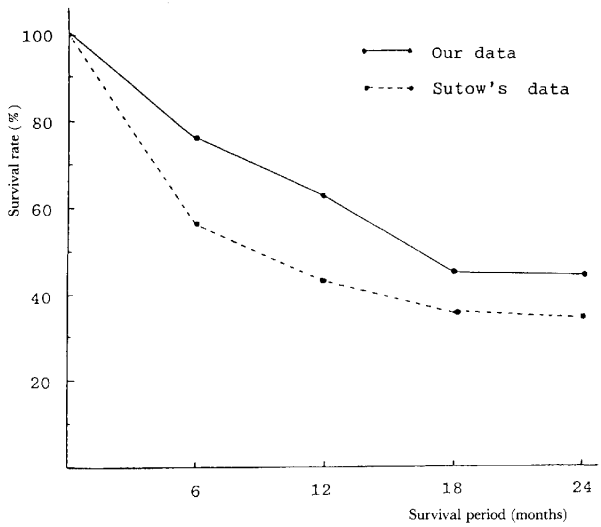


Fig. 4. Survival rate of neuroblastoma (33 cases) in Korea, compared with Sutow's data (25) (142 cases) in the U.S.A.

jority of patients (15). In the past, a surgical amputation usually offered only slim chance of survival, although often with the pain of disfigurement and death.

Surgery and postoperative chemotherapy for osteogenic sarcoma during 1975-1980 yielded 55 % survival (16). In the adjuvant chemotherapy program, the patients had amputation or disarticulation for the primary lesion when they had no demonstrable metastasis at the onset of treatment. Chemotherapy was initiated after recovery from surgery, generally within 14 days postoperatively. Adriamycin was administered at 30-40 mg/m^2/day for 3 successive days and repeated every 4 weeks (total cumulative dose 550 mg/m^2). Six among 11 patients have been disease-free for more than 2 years. The primary sites of long-term survivors were distal femur (4 cases), proximal tibia (1 case) and humerus (1 case). Five of 11 patients had relapses in the lungs (4 cases) and amputation site (1 case).

Systemic chemotherapy with adriamycin for the patients with lung metastasis, who were referred from other hospitals after surgery, produced a cure rate of 20 %. One among 5 patients with metastasis was cured with adriamycin and is alive for 7 years without recurrence (Fig. 5-a, b) (16).

Chemotherapy for histiocytosis. This group is characterized by localized or disseminated infiltration by benign or malignant histiocytes. It includes eosinophilic granuloma, Hand-Schüller-Christian disease, Letterer-Siwe disease and histiocytic medullary reticulosis (HMR). In Korea, there is an increasing number of children with histiocytosis who have responded favorably to therapy and appear to be cured. We analyzed and calculated the survival rates of the 34 patients with histiocytosis treated from January 1975 to December 1981 (17). Seven cases (20 %) of eosin-

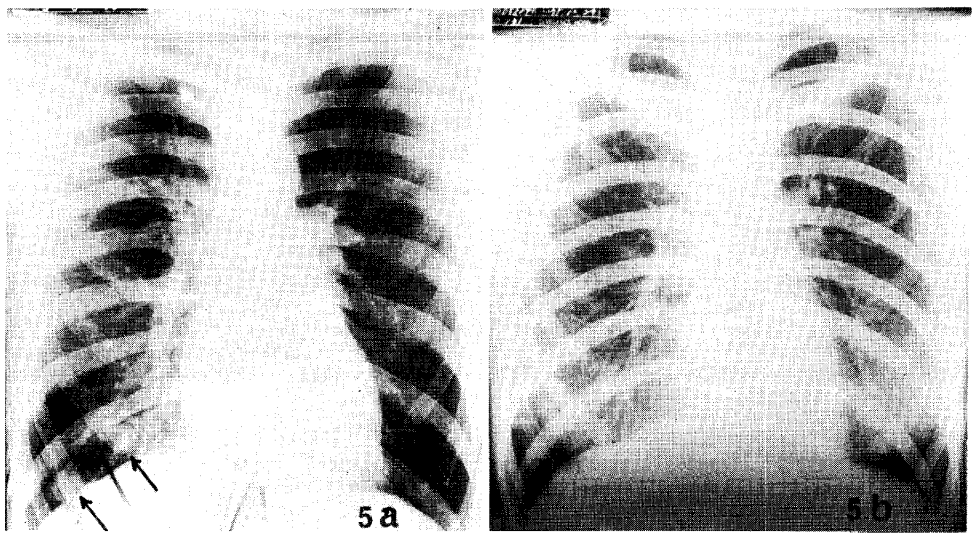


Fig. 5. (a) Chest x-ray showing pulmonary metastases of osteogenic sarcoma (arrows). Tomograms revealed multiple bilateral metastases. (b) Three months after therapy, the chest x-ray became normal with no residual lesion.

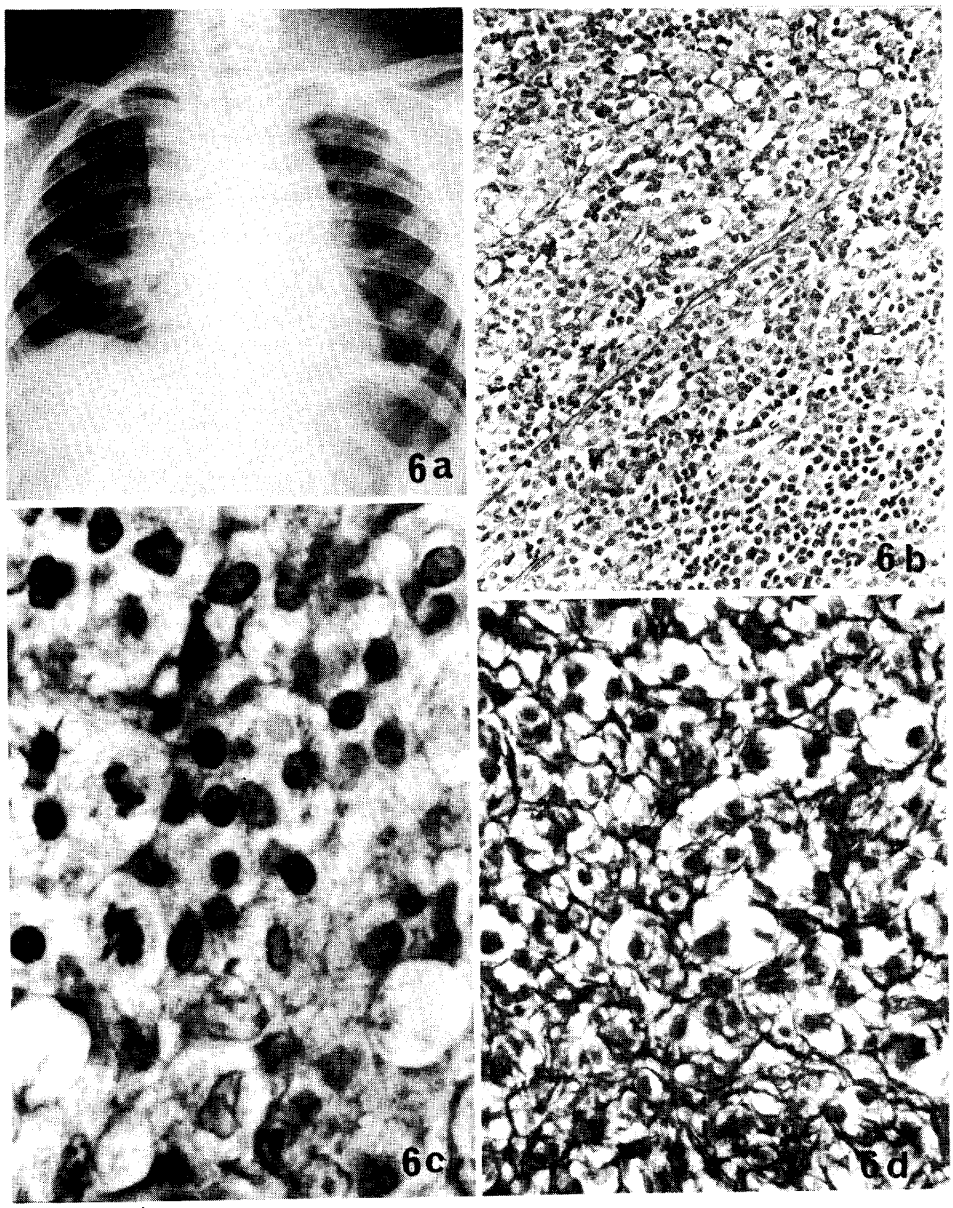
ophilic granuloma were seen in older children. Eleven cases (32 %) of Hand-Schüller-Christian disease began at 2 to 3 years of age. Eleven cases (32 %) of Letterer-Siwe disease were found, usually during the first year. The onset of five cases (15 %) of HMR was between ages 5 and 14.

The principal symptoms of eosinophilic granuloma and Hand-Schüller-Christian disease were related to bone. The symptoms of Letterer-Siwe disease and HMR were persistent high fever, hepatosplenomegaly and pancytopenia. In particular, Letterer-Siwe disease developed a high incidence of skin rash and purulent otitis media.

Of the 13 cases with eosinophilic granuloma or Hand-Schüllar-Christian disease treated by surgery or surgery plus irradiation of 600 rads, 6 cases have been cured. Patients with Letterer-Siwe disease were initially treated with combination chemotherapy consisting of vinblastine (3-5 mg/m^2 weekly) and prednisolone (40 mg/m^2 daily). Patients were treated for 8 weeks unless there was rapidly progressive disease after 4 weeks of therapy. The maintenance program during remission has not yet been determined at our clinic. Only one patient had partial remission and the remaining patients died.

Combination chemotherapy for HMR, such as vinblastine (3-5 mg/m^2, 2 times weekly) and prednisolone (40 mg/m^2, daily), produced complete remission in 3 among 5 patients. Patients were treated with the above combination for induction of remission for 4 weeks unless there was rapidly progressive disease during chemotherapy. After remission was achieved in 4 weeks, vinblastine was given at a dosage of 3-5 mg/m^2 weekly for 18 months as maintenance program. Of two among 3 patients who acquired remisson, one patient without maintenance died of recur-

rent disease 6 months later, and another patient died of relapse 18 months later despite maintenance treatment. A six-year-old girl has been disease-free for over 4 years, and for 2 years since the end of maintenance therapy (17). This girl was admitted on June 16, 1979 due to persistent high fever and cough for 1 month. She had no history of recent viral illness. X-ray examination showed massive supraclavicular lymphadenopathy and mediastinal widening (Fig. 6-a). The supe-



rior mediastinal syndrome with severe respiratory distress and facial edema developed. The liver was palpable 3 cm below the right costal margin. Hematologic evaluation revealed anemia (Hb, 10 g/dl) and leukopenia (WBC, 2,800/μl). Cervical lymph node biopsy was compatible with HMR (Fig. 6-b, c, d).

DISCUSSION

The etiology of most tumors in childhood is obscure. The epidemiologic study of cancer patterns will lead to the formulation of possible etiologic relationships. The majority of neoplasms in the pediatric age group in Korea are mesenchymal, the most common tumors being leukemia, malignant lymphoma and embryonal tumors such as Wilms' tumor and neuroblastoma. With some exceptions, the occurrence of these neoplasms in Korea does not strikingly differ from those in Japan and the U.S.A.

The relatively high frequency of myelogenous leukemia and non-Hodgkin's lymphoma in Korea, which is similar to Japan, may be ascribed to a genetic factor which plays an important part in etiology. It has been consistently shown that liver cancer is very common in children in Korea (4). Although further investigation is required, hepatoma occurs in children born to a hepatitis-B virus-infected mother due to neonatal hepatitis through intra-uterine virus transmission. This preliminary observation suggesting that transplacental carcinogenesis occurs in children opens new vistas to the prevention and control of childhood hepatoma.

Ever since Farber (5) reported in 1948 that remission was induced in acute leukemia with aminopterin, the concept of an optimal therapeutic regimen with many effective chemotherapeutic compounds has changed significantly. The advances in antileukemic therapy would be impossible, if multimodality treatment were not introduced. The development of effective combination chemotherapy to obtain remission and to maintain longer periods of remission resulted in a 20 % cure rate in ALL. The most significant contribution was therapy devised to eradicate disease in pharmacological sanctuaries. Over 50 % of the children who do not receive prophylactic CNS therapy at the time of induction develop CNS relapse, compared with an incidence of 5 to 10 % in those patients who receive prophylactic therapy. Most children with ALL which involved CNS died of bone marrow relapse (18). Supportive care, including improved transfusion therapy and antimicrobial agents, has also been extremely valuable to improve the cure rate of acute leukemia (19).

Fig. 6. (a) Chest X-ray of a patient with histiocytic medullary reticulosis showing massive hilar and mediastinal lymphadenopathy and interstitial infiltration. (b) A lymph node showing diffuse, complete infiltration of sinuses with atypical histiocytes having numerous mitoses (H.E. × 100). (c) Higher magnification of the lymph node showing bizarre histiocytes with abundant, clear cytoplasm with phagocytic debris (H.E. × 1,000). (d) Well-developed reticulin fibers surrounding a single histiocyte (silver, × 400).

The results of our therapy are inferior to those of developed countries like Japan or the U.S.A. The comprehensive protocol of ALL and optimal supportive care in advanced countries has resulted in a 3-year survival rate of over 70 % (20). In Korea, the financial burden to provide intensive chemotherapy and optimal supportive care for acute leukemia patients adds unnecessary distress to families and physicians.

In order to improve the cure rate in ALL, we need more social and governmental support to administer more effective comprehensive chemotherapeutic regimens and also more oncologists to participate in the management of cancer patients. Prior to our report, there was no systemic research on childhood leukemia. We would like to emphasize that this is the first paper in Korea on the survival rate of ALL treated with the multimodality method.

Ever since Farber (21, 22) first treated Wilms' tumor with a multimodality approach and reported a complete cure rate of 80 %, researchers have provided new information for reassessment of our current understanding of Wilms' tumor. A better survival rate has been achieved and therapy has been refined so that excess treatment in early stage disease and in cases with a favorable histology can be reduced without jeopardizing cure rate (23).

Recently the U.S. National Wilms' Tumor Study has made a great contribution to the refinement of treatment method. It developed a classification of Wilms' tumor in order to correlate the histologic pattern with clinical response to therapy. About 12 % of tumors had focal or diffuse anaplasia, or had sarcomatous features. Because patients with this kind of tumor showed poor survival, these tumor types were categorized as "unfavorable histology". The remaining 88 % of tumors were designated as "favorable histology". In a review of 477 cases from the National Wilms' Tumor Study, the 2-year survival of relapse-free cases was 89 % among cases with favorable histology, compared with 29 % among cases with unfavorable histology. Notable among the many prognostic factors is the cytohistologic pattern of tumor. Patients with unfavorable histology have a much worse prognosis. The two-year survival rates for those with and without positive lymph nodes were 54 % and 82 %, respectively (24).

The above data have made it possible to modify therapeutic strategy and follow-up according to accurately defined risk factors, and to reserve intensive chemotherapy and radiotherapy for patients of high risk. This therapeutic strategy results in fewer short- and long-term complications of treatment for patients who do not require such aggressive management. Now, we plan to shorten the duration of treatment from the present 18 months for post-operative chemotherapy to 6 months, and add adriamycin to the chemotherapy protocol for high risk cases of Wilms' tumor.

The prognosis in neuroblastoma has not improved in recent years. The two-year overall survival rate is the same today as it was prior to the use of intensive chemotherapy. Despite widespread and intensive use of multi-drug programs,

there has been little indication of alteration of the survival rate (25). The striking finding of neuroblastoma is that factors such as age at diagnosis, stage and histology of tumor influence prognosis (26, 27). The patients included in this study are generally similar to other series except for the high incidence of stage IV patients (57 %). Decreasing survival is seen universally as the age at the time of diagnosis increases. The survival difference is marked and suggests an important age-dependent factor either in tumor cell maturation or clinical behavior, which is worthy of further study. The Evans' staging system has good clinical correlation as noted by others (28). This study of 33 patients confirms that the clinical stage and age at onset have a large influence on survival in neuroblastoma.

The site of origin of neuroblastoma has also been considered as a factor influencing survival. Although survival is inversely correlated with patient's age at diagnosis, this phenomenon of survival in the case of mediastinal neuroblastoma was not so striking as that seen in patient with neuroblastoma originating in other sites. Overall survivals of patients with mediastinal neuroblastoma in other series were between 50 % and 85 % (29, 30). Our data confirm these findings. These studies indicate that mediastinal neuroblastoma can be successfully treated even if the tumor has spread and occurs in old age, whereas abdominal neuroblastoma in old age ordinarily has poor prognosis. Interestingly, spontaneous maturation and regression occur at a much higher rate in cases of neuroblastoma than any other tumor (31). Prognosis may also be influenced by degree of histologic differentiation. Lymphocyte infiltration or cellular differentiation of tumor is important for spontaneous regression in stage IV cases (32, 33). In addition, tumor specific antigen of neuroblastoma stimulates antibody formation, and T-cells of surviving cases of neuroblastoma possess cytotoxicity against neuroblastoma cells *in vitro* (34). Further study is required as to possible enhancement of the immune reactivity of these patients in order to obtain clinically beneficial effect.

Recent studies of osteogenic sarcoma suggest the principle use of postoperative chemotherapy in patients apparently free of cancer but with a high likelihood of recurrence. In the usual course of this disease, surgical resection of the primary tumor is followed within 6 months by development of metastatic disease in the lungs in more than 50 % of patients. After detection of metastasis, 90 % of the patients die within one year.

However, dramatic results in cases with osteogenic sarcoma were described by Jaffe *et al.* (15) in 1973, utilizing massive doses of methotrexate with folinic acid rescue. The new aggressive approach for metastatic osteogenic sarcoma resulted in a remission rate of 35 %. Due to the high cost of this regimen, it is not practical in Korea. The second effective chemotherapy regimen for osteogenic sarcoma consists of adriamycin. Cortes *et al.* (35) reported responses in 7 of 17 patients (41 %) with pulmonary metastasis. This method is reasonably simple and of low cost, and can be applied as postoperative adjuvant systemic therapy in Korea. The encouraging responses obtained with adriamycin and high doses of metho-

trexate have provided extensive information on combination multi-drug chemotherapy (36, 37), and suggest that pretreatment with intensive chemotherapy can allow the surgeon to consider limb salvage in certain instances (38, 39).

Histiocytosis is a disease involving a wide spectrum of histiocytic disorders. The clinical manifestations of children with histiocytosis are as varied as the pathologic spectrum of disease itself. Histiocytosis ranges from an isolated, slow-growing lesion to aggressive, widely disseminated malignant disease with a fatal outcome. Patients with unfavorable histology, such as the infiltration of atypical histiocytes and their precursors in liver, lung or bone marrow, respond poorly to therapy. The treatment of Letterer-Siwe disease resulted in no survival, which is in marked contrast to the results of Lahey (40) but similar to those of Croker (41).

For the definitive diagnosis of HMR, it must be distinguished from benign diseases such as virus-associated hemophagocytic syndrome. The most important features distinguishing the virus-associated hemophagocytic syndrome from HMR are the cytologic characteristics of the proliferative histiocytes. Virus-associated hemophagocytic syndrome consists of mature histiocytes. Marked hemophagocytosis by histiocytes is invariably present and is most prominently observed in bone marrow aspirate. Cells with neoplastic characteristics are not present. The diagnosis of HMR is most readily established by examination of lymph nodes, spleen or liver, in which proliferating histiocytes have neoplastic characteristics. Bone marrow involvement by HMR is seen in less than one-fourth of patients (42, 43).

In Korea, the treatment, much less cure, of pediatric cancer was virtually unknown until 10 years ago. There were some pitifully inadequate attempts at cure by surgery. The recent improvement in economic standards and the expansion of the National Medical Insurance have provided easier access to hospitals resulting in a larger number of admissions, and more opportunity for medical personnel to provide the best therapy possible. This increase in emphasis on pediatric cancer therapy disclosed the fact that knowledge and experience in this field was practically non-existent. To fill this need, the division of Pediatric Oncology of Yonsei University Cancer Center was created in 1974. This Center fulfills many roles such as the education of doctors and students, and acts as a nationwide referral center for cancer research on different therapeutic approaches which have been developed.

We realize that various protocols are currently used throughout the world. However, since Korea's cultural and economic circumstances have created a unique health care system, we must develop our own approach to the treatment of pediatric cancer. We are speaking of a new era of cautious optimism in treatment of children with cancer through multiinstitutional cooperation.

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