Original Article

Cancer in infancy: Experience of Children Welfare Teaching Hospital, Medical City Complex, Baghdad

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Summary:

Background: It is becoming increasingly apparent that the study of infant cancer may lead to further understanding of the mechanisms of carcinogenesis, due to the unique clinical, genetic, and epidemiologic characteristics of cancer in infant.

Objectives: To study the clinical and pathological presentation of infants with cancer, their outcome and survival.

Patients & methods: A retrospective study was done over a 6 years period between (Jan.1st.2001- Dec. 31st. 2006), reviewed the records of 85 infants diagnosed and treated in oncology unit, children welfare teaching hospital, medical city-Baghdad.

Results: The majority of patients 57(67%) were from Baghdad & surrounding provinces; Leukemia was the most common type of cancer reported in 26(30.5%) infants followed by Neuroblastoma in 25(29.4%) infants. Males were more common than females with a ratio of 1.5:1 with duration of onset more than one month in 60(72.3%) patients. Pallor & fever were the most common presenting symptoms in 56(65.8%) and 43(50.5%) patients respectively. Bone marrow was the most common site of involvement in 31(36.4%) patients. Event free survival in treated patients was 16.4% with high rates of death (32.9%) and patients lost to follow-up were 24(28.2%).

Conclusions: The study showed low event free survival due to high mortality rate due to lack of adequate supportive care, intensive care unit, bone marrow transplant facility and abandonment of treatment.

Keywords: Cancer, infants, outcome.

J Fac Med Baghdad 2015; Vol.57, No .1
Received Jun 2014
Accepted Dec.2014

Introduction:

Adult cancer usually form in epithelial tissues and are believed often to be the result of a long biological process related to the interaction of exogenous exposures with genetic and other endogenous characteristics among susceptible people. However, in young children, particularly infant, the aberrant genetic process that fail to safeguard against the clonal proliferation of cell with unregulated growth potential occur very early in life and progress very quickly. Due to the unique clinical, genetic, and epidemiologic characteristics of cancer in infant, it is becoming increasingly apparent that the study of infant cancer may lead to further understanding of the mechanisms of carcinogenesis. (1) Although it is a rare event in infant, the process of oncogenesis occurs in close temporal relation to embryogenesis. Factors that should be considered as causes of cancer in infants include genetic susceptibility, acquired or constitutional; parental, intrauterine, and immediate postnatal environmental exposures, and transplacental metastasis.(2) Malignancies of infancy represented 10% of all cancer that was diagnosed among children younger than 15 years of age. Neuroblastoma comprised 28% of infant cancer cases and was the most common malignancy among these young children (65 per million infants). The leukemias as a group (41 per million infants) represented the next most common type of cancer, comprising 17% of all cases. (3) Leukemia in infants differs from leukemia in older children with variation in type of diagnosis [acute myeloid (AML) acute lymphoblastic (ALL)], clinical symptoms, tumor genetics and response to treatment. (4) The average annual incidence rates for malignant germ cell and malignant soft tissue tumors were essentially the same each comprised about 6% of infant cancer. (3)

Patients and methods:

From 1st Jan. 2001 to the 31st Dec. 2006, 85 patients below 1year of age admitted to Children Welfare Teaching Hospital in Medical City/ Baghdad and diagnosed to have malignant diseases, were enrolled in this retrospective study.The information regarding (age, sex, residence, weight, date of diagnosis, clinical presentation, diagnostic methods, date of starting treatment, response to treatment and its complication, date of last follow up, and outcome) was taken from the inpatient

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files and from the records of the oncology consultation clinic. The diagnosis was established by the following procedures according to the type of the disease. Examination of bone marrow aspirate for patients in whom there was a suspicion of leukemia by finding of blast cells in the peripheral blood film. From 17 patients with acute lymphoblastic leukemia (ALL); 16 patients were diagnosed by bone marrow aspirate (BMA) and one patient was diagnosed by peripheral blood film only because BMA was diluted twice.Four patients with acute myelogenous Leukemia (AML) were diagnosed by BMA. From five patients with presumed diagnosis of Juvenile Chronic Myelogenous Leukemia (JCML), 4 cases were diagnosed by peripheral blood film and BMA and one by peripheral blood film only because BMA was inadequate.From twenty five patients with Neuroblastoma (NB); 10 were diagnosed by surgical biopsy, 7 by fine needle aspiration (FNA), and 6 by bone marrow aspiration (BMA), one by BMA and FNA, and one by BMA and biopsy.Thirteen patients with Wilms' Tumor (WT); 7 were diagnosed by surgical biopsy, 3 by FNA, 2 by biopsy and FNA and 1 by Ultrasound only because the patient died in surgical unit before operation. Eight patients with Hepatoblastoma (HB); 6 were diagnosed by FNA and 2 by opened biopsy. Opened Biopsy also was used for diagnosis of 6 patients with Rhabdomyosarcoma (RMS), 5 patients with Germ cell tumor (GCT) and 2 patients with Retinoblastoma (RB).

Statistical analysis:

Patient data were tabulated and processed using SPSS (Statistical Package for the Social Sciences 13.0) for windows. (5) Qualitative data are expressed as frequency and percentage, quantitative data as mean and median. Chi-square test was used to identify P-values. P-values equal or less than 0.05 were considered significant.

Results:

A retrospective analysis identified 85 patients that met the criteria of the study (hematological malignant diseases or solid tumors) who were 1 year old or younger.Table 1 shows the types of infantile malignant diseases and its frequency; leukemias (30.5%) followed by neuroblastoma (29.4%) and Wilms' tumor (15.3%). The detailed characteristics of the 85 patients are shown in table 2 and 3. The median age was 7 months (range from 1 month to 12 months) the mean age was 7.1 months. The median duration of signs and symptoms was 41 days, range 4 days to 9 months. The most common presenting symptoms were pallor 56(65.8%) abdominal distension 43(50.5%), fever 43(50.5%) and lymphadenopathy 19(22.3%). The median length was 66 cm (range from 60 to 99 cm) with mean of 64.1 cm. the median weight was 7.5 Kg (range 3-10 Kg).

Treatment outcome: From 85 patients, 21 patients didn't receive treatment (12 did not receive treatment by family request, 5 patients died before treatment, and 4 patients were lost to follow-up). Table 4 From 64 patients who received induction chemotherapy, 24(37.5%) got remission, 14(21.9%) had partial response, 9(14.1%) abandoned treatment, 17(26.6%) died. The 24 patients who were in remission state continued treatment with chemotherapy, 14 (58.3%) patients were in continuous complete remission state, 5(20.8%) patients had relapse (3 of them were lost, one of them died and another continued on palliative treatment), 2(8.3%) abandoned treatment, 1(4.1%) patient had treatment toxicity and 2(8.3%) patients were lost after complete treatment. From 14 patients with partial response, 4(28.5%) patients were retreated and fate of them was as follow: Two patients died, one patient lost to follow-up one patient had complete response. Four patients (28.5%) continued on palliative treatment and their fate was as follows:

Three patients lost, one patient died. Four (28.5%) patients abandoned treatment and 2 (14.28%) patients died. Table 5 shows summary of treatment and outcome for each disease.

Table 1. Frequencies of malignant diseases

Type of malignant disease	Frequency	Percent (%)
Leukemias	26	30.5
Neuroblastoma	25	29.4
Wilm's tumor	13	15.3
Hepatoblastoma	8	9.4
Rhabdomyosarcoma	6	7.1
Germ Cell Tumor	5	5.9
Retinoblastoma	2	2.4
Total	85	100.0

Table 2. Demography of 85 patients with infantile malignant diseases

Demographic variable	No.	% (valid %)
Overall	85	100
Age (months)		
<6	30	35.3
6-12	55	64.7
Sex *		
Male	51	60
Female	34	40
Duration of onset (months)		
<1	23	27.1(27.7)†
1-3	48	56.5(57.8)
>3	12	14.1(14.5)

* Male: female ratio 1.5:1

† Two patients were not mentioned in the record.

Table 3. Clinical manifestation*

Clinical manifestation	No.	% (valid %)
Pallor	56	65.8
Fever	43	50.5
Abdominal mass	43	50.5
Hepatomegaly ≥ 5 cm BCM	30	35.2
Lymphadenopathy	19	22.3
Vomiting	11	12.94
Bleeding	10	11.7
Skin rash	6	7.05
Proptosis	3	3.5
Jaundice	3	3.5

* Patients usually present with more than one clinical feature.

Table 4. Treatment details and results of 85 patients

	No.(%)
Treated	64(75.2)
Not treated	21(24.7)
Total	85 (100)
Treatment phase	
Induction phase	
Complete remission	24(37.5)
Partial response	14(21.9)
Abandonment of treatment	9(14.1)
Died	17(26.6)
Total no.	64(100)
Post remission phase	
Event free survival	14(58.3)
Relapse	5(20.8)
Abandonment of treatment	2(8.3)
Lost to follow up post finishing treatment	2(8.3)
Treatment toxicity	1(4.1)
Total no.	24(100)
Fate of partial response	
Reinduction	4(28.5)
Palliative treatment	4(28.5)
Abandonment of treatment	4(28.5)
Died	2(14.2)
Total no.	14(100)

Table 5. Summary of treatment and outcome

Diseases	Patient	Died before treatment	Not received treatment	Died during treatment	Lost to follow up	Off treatment in remission
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL*	17(20)		2(11.7)	7(41.1)	6(35.2)	1(5.8)
AML	4(4.7)	2(50)	2(50)			
CML	5(5.8)		5(100)			
NB	25(29.4)		2(8)	8(32)	6(24)	9(36)
WT†	13(15.3)	2(15.3)	1(7.6)	2(15.3)	5(38.4)	2(15.3)
HB	8(9.4)	1(12.5)	2(25)	3(37.5)	2(25)	
RMS	6(7.1)		1(16.6)	1(16.6)	4(66.6)	
GCT	5(5.9)			2(40)		3(60)
RB	2(2.4)				2(100)	
TOTAL	85	5(5.8)	16(18.8)	23(27.05)	24(28.2)	15(17.64)

*One patient continued on palliative treatment.
†One patient had treatment toxicity.

ALL (acute lymphoblastic leukemia), AML(acute myeloid leukemia), CML(chronic myeloid leukemia), NB(neuroblastoma), WT(wilms tumor), HB(hepatoblastoma), RMS(rhabdomyosarcoma), GCT(germ cell tumor), RB(retinoblastoma),

Discussion:

Malignant disease in the infancy period has unique spectrum and clinical aspect as compared to the older children. Due to the immature physical developmental state and organ function, the dosage of medication and the choice of therapy often have to be modified. (6) The percentage of infantile malignancy was (5.48%), which was lower than in M.HS study(7) which was done in South India during (2003-2006) and G.Chan study(6) in Hong Kong during (1989-1998) in which the percentage of infantile malignancy was (11%) & (13.5%), respectively. This difference might be due to the fact that large number of childhood cancers remains undiagnosed due to limitations of diagnostic facilities, or under registration and because we do not receive or treat cases of CNS malignancies. Leukemia was diagnosed in 26 (30.5) of cases, followed by neuroblastoma 25 (29.45%) and Wilms tumour in 13 (15.3%) this was similar to G.Chan study(6) results in which leukemia was the commonest malignancy in 8 (20%) of cases followed by neuroblastoma and Wilms tumour in 2 (5%) of cases and also similar to M.HS study(7) in which leukemia was the most common malignancy in (30%) of cases followed Wilms tumor in (12%) and neuroblastoma in (10%) of cases, but it differs from that mentioned in NCI study during (1976- 1984) and (1986-1994) (3), in which neuroblastoma was the most common infantile malignancy in (28%) of cases followed by leukemia in (17%) of cases; this might be due to under diagnosis of cases with NB stage IVs. Male to female ratio was 1.5:1 which was similar to G.Chan study [6] but differs from in NCI study (3) in which males and females were equally affected. The overall survival rate was (17.6%) which was lower than that mentioned in G.Chan study(6) (73%) and that mentioned in Yang study (8) in Hong Kong during (1995-2001) (61%); this big difference due probably to high percentage 24(28.2%) patients were lost to follow up and 16 (18.8%) patients did not receive treatment either due to difficulties in transport, poor socioeconomic status, ignorance in addition to those who died before treatment due to advanced stage of the disease 5(5.8%). Some types of malignancies; like lymphoma and bone tumors are not present because these tumors are extremely rare in infants. (3)

Leukemias: It was diagnosed in 26 (30.5%) of cases; this is slightly less than a figure in S. AL. Hadad study (1995-2000) which was (31.5%)(9) with male predominance in (77%) than

female (23%), this result was different from that mentioned in Ba-Saddik IA study in Yemen 2013(10) that showed female predominance in (66.7%) than male (33.3%). Leukemia in this age group is associated with poor prognosis as shown in studies done in different centers, where the survival rate was 5.8%, while in S.AL.Hadad study (1995-2000) the survival rate was (zero)(9) , in G.Chan study was (44%)(6) and (33%) in NCI study(3).

Neuroblastoma (NB) :Twenty five patients (29.4%) was diagnosed with NB, with male and female are equally affected, this result was different from that mentioned in Ba-Saddik IA study in Yemen2013(10) in which males are predominantly affected in this type of blastoma Wilms tumor (WT) was diagnosed in 13(15.3%) case which is slightly higher than the figure from S. AL.Hadad study (1995-2000) which was 8 (14.03%)(9), a study done in India by M.SH(7) (2003-2006) rate was 12% and in study by G. Chan (1989-1998)(6) rate was 2(5%) patients, this higher rate may be because the place of the study is a major referral center for all types of cancer in children. Males were affected more than females in (61.5%) for males and (38.5%) for females and this different from than that mentioned in Ba-Saddik IA study in Yemen2013(10) in which females were predominantly affected. However the survival rate in our study is still low (15.3%) this is most probably due to lack of multidisciplinary team work required for such type of cancer.

Heptoblasoma (HB): In this study it was diagnosed in 8 (9.4%) cases which is slightly higher than that in S.AL-Hadad study which was 4 (7.01) (9)and study done in India by M.SH. (2003-2006) which was (2%). (7) Males and females were equally affected; this result was different from that mentioned in Ba-Saddik IA study in Yemen 2013(10) in which males were predominantly affected. Survival rate was low because 3/6 patients who received treatment died during treatment and other 3 patients were lost to follow up, in a study done by G. Chan (1989-1998) the survival rate was more than (90%).(6) This poor out come in our cases may be related to delay in diagnosis and referral of the cases in very advanced stages of disease, in addition to family ignorance and poor compliance to treatment.

Rhabdomyosarcoma (RMS): Diagnosed in (7.1%) 6 which is less than the rate in S.AL-Hadad study (1995-2000) which was(9) (8.77%)5 but in both studies the rate was higher than other study like that done by Yang (1995-2000) rate was 1(1.2%) patient (8), this may be due to type of referral cases, or to difference in genetic factors because RMS usually have some type of chromosome abnormality in the cells of the tumor, which are responsible for the tumor formation.(11) Males were affected more than female in (83.3%) for males and (16.7%) for females and this was similar to that mentioned in Ba-Saddik IA study in Yemen2013(10) in which males were predominantly affected. Survival rate in our study was (zero) because 1/ 5 patients died during treatment and 4 patients lost to follow up. Germ cell tumor (GCT) was diagnosed in 5(5.9%), this is similar to rate in NCI study which was (6%) (3) & less than the rate in G.Chan study (1989-1998) which was 7(17.5%)(6). Females were more affected than males in (60%) for females and (40%) for males. GCTs except malignant teratoma is chemo and radiation therapy sensitive (6), This goes with high survival rate in G. Chan study (1989-1998) which show that the event free survival rate was (85%) (6) ,and in our study the rate was (60%).

Retinoblastoma (RB): In retinoblastoma with early detection, local eye-saving treatment (laser or local irradiation) may be possible.(6) RB was diagnosed in 2(2.4%), this rate is low in comparison with rate in other studies like NCI study (12%)(3), in G. Chan study 3(7.5%)(6), in M.HS study (6%)(7), this low rate may be because most of the cases are treated and followed in ophthalmology centers except for patients with metastatic RB where chemotherapy is usually not indicated(6), or because of delay in diagnosis until after 1 year of age.Males and females were equally affected; this was different from that mentioned in Ba-Saddik IA study in Yemen 2013(10) in which females were predominantly affected. Survival rate in our study were low because the two patients who were diagnosed and treated were lost to follow up. The treatment in form of chemotherapy and other supportive therapy were received in the oncology unit which is part of Children Welfare Teaching Hospital, in case of complications and critical cases all were treated in the same unit; as we do not have specialized intensive care unit.

Conclusions:

Males were more common affected than females, with leukemia being the most common type of cancer in this age group. A relative long duration of onset with high rate of bone marrow involvement in infants with solid tumors due to late presentation. Low event free survival was due to large number of patients who were lost to follow-up and high mortality rate due to inadequate supportive care capabilities, and inavaialabilty of bone marrow transplant for resistant / relapsed cases.

Authors Contribution:

Study conception and design: Salma Al-Hadad

Acquisition of data analysis: Samher Thamer, Dr. Amir Al-Darraji

Interpretation of data, drafting of manuscript and critical revision: Salma Al-Hadad , Raghad Al-Saeed

References:

1. *Kenney LB, Beaman GH; Special considerations for the infant with cancer.in Pizzo P, Poplack D, Eds. Principles and Practices of Pediatric Oncology. 3rd ed. Philadelphia, PA: Lippincott-Raven; 1997:343-356.*
2. *Reaman GH, Bleyer A. infants and adolescents with cancer: special consideration. Pizzo PA, Poplack G (eds). In: principles and practice of pediatric oncology: 4th ed. Lippincott Williams and Wilkins, PA, 2002: p409-420.*
3. *James G. Gurney, Malcolm A. Smith, Julia A. Ross. Cancer Among Infants 1999;X11:149-155.*
4. *Susan E. Puumala, Logan G. Spector, Melani M. Wall, et al, Infantile leukemia and parental infertility or its treatment: a Children's Oncology Group report, Human Reproduction; 25 (6): 1561-68, 2010 [IVSL, highwire]*
5. *Nourusis MJ. APSS statistical software. SPSS:Base and Advanced statistics[computer program]. Version 13.0. Chicago, SPSS Inc, 2004.*
6. *GCF Chan, SY Ha, KL Chan, et al. Malignant Neoplastic Diseases Diagnosed in the Infancy Period. HK J Peadiatr 1999;4:25-31.*
7. *M.HS,B. Aruna Kumari,L. Appaji, et al. Profile of infantile malignancies at tertiary cancer center –A study from south India. Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part 1.Vol 25,No.18S(June 20 Supplement),2007:2002-6.[IVSL, highwire]*
8. *Yang, Chao-Ping, Hung, et al. Cancer in Infant :A review of 82 cases. Pediatric Hematology and Oncology 2005 Sep;22(6):463-481.*
9. *Sadiq,Z.M,AL-Hadad,S.A.,Farhan,M.F.,Cancer in Infancy, clinic- pathological feature ,J fac med Baghdad, 2004;46 (3-4):145-149.*
10. *Ba-Saddik IA. Childhood cancer in Aden, Yemen. Cancer Epidemiol. 2013 Dec; 37(6):803-6.*
11. *Rhabdomyosarcoma, Health resources centre, Virginia common wealth University health system. [online]. Cited [2009 Feb 25]; available from http: URL://www.vcuhealth. org/greystone/?pageid=P02743.*