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Prognostic implication of serum Alpha-fetoprotein response to neoadjuvant chemotherapy in hepatoblastoma patients

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***Abstract*---**Objective: This retrospective study aims to identify the early changes in serum alpha-fetoprotein levels (AFP) and their correlation with the survival outcome of hepatoblastoma patients. Materials and Methods: A total of 68 patients presented to the children's cancer hospital Egypt and the national cancer institute from January 2013 till June 2016 were included in this study. Results: AFP level was measured post-cycle 2 in 60 patients; 44 (73.3%) patients showed a decline in AFP level by >1 log reduction. The 3-year EFS was 75.6% for patients with >1 log reduction in AFP level, compared with 36.5% for those with <1 log reduction (p=0.010). The 3-year OS' for patients with >1 and <1 log reduction in AFP level were 80.4% and 39.4%, respectively (p=0.005). On multivariate analysis; Patients with AFP log reduction< 1 had worse OS/EFS with hazards ratio (HR): 3.9 and 95% confidence interval (CI):1.4-11.2, p value=0.011 and HR: 3.2 and 95% CI: 1.3-8.9, p

value=0.013 respectively. Conclusion: The ease of AFP determination makes it a valuable tool that could be routinely used to evaluate the therapeutic efficacy and predict the survival outcome.

***Keywords*---**Alpha-fetoprotein, Childhood, Hepatoblastoma, Neoadjuvant Chemotherapy, Prognosis.

Introduction

Hepatoblastoma (HBL) is the most common pediatric liver tumor and is usually diagnosed before five years of age. It accounts for 1.2% of malignancies in patients less than 15 years of age [1]. Complete surgical resection is essential for the cure of hepatoblastoma, but unfortunately, only about one-third of the patients with HBL have a resectable tumor at the time of diagnosis [2]. AFP is very high in neonates and steadily falls after birth, the half-life of AFP ranges from 5 to 7 days, and by the age of 1 year, it reaches the normal adult level of 10ng/dl [3]. Alpha-fetoprotein (AFP) levels at diagnosis have been reported as a prognostic factor, AFP levels less than100, AFP 100-1000, AFP>1 million are associated with poor prognosis [4]. Several studies have discussed the prognostic value of early dynamic changes in serum AFP levels. The objective of this study was to clarify whether the AFP reduction rate during neoadjuvant chemotherapy offers a prognostic factor for hepatoblastoma in our patients.

Methods

From January 2013 to June 2016, seventy-three hepatoblastoma patients were treated at the children's cancer hospital Egypt and the national cancer institute.
For this analysis, five patients who underwent upfront complete tumor resection were excluded. Sixty-eight patients was included in this study; the data of these patients were retrospectively retrieved from their medical records.

Treatment

Our treatment protocol was based on the COG AHEP 0731 trial protocol. Patients were staged at diagnosis using the Evans staging system, while the PRETEXT staging system was used to assess tumor resectability. A total of 6 cycles of chemotherapy were given for patients with unresectable hepatoblastoma at diagnosis. Each cycle lasted for 21 days. The chemotherapy regimen included cisplatin intravenous (IV) over 6 hours, 100 mg/m^2/dose [3.3 mg/kg/dose for patients <10 kg] on day 1, with hydration over 24 hours; 5-fluorouracil (slow IV push over 2-4 minutes, 600 mg/m^2/dose [20 mg/kg/dose for patients <10 kg]) on day 2; and vincristine (IV push over 1 minute, 1.5 mg/m^2/dose [0.05 mg/kg/dose for patients <10 kg (maximum dose: 2 mg)]) on days 2, 9, and 16 and doxorubicin (IV over 15 minutes, 30 mg/m^2/dose [1 mg/kg/dose for patients <10 kg] on days 1 and 2).

Surgical resection was done after 2 or 4 courses of chemotherapy, patients who were unresectable after 4 courses of chemotherapy were considered refractory. To investigate the prognostic significance of AFP, we measured AFP levels at presentation and changes in AFP levels after the second cycle of chemotherapy. A

Favorable initial response was defined as a ≥1 log decline in the AFP level (more than 90% decrease from the initial level). Tumor response was reevaluated after the first two courses using Response Evaluation Criteria in Solid Tumors; if still unresectable, another two cycles were administered (RECIST) [5].

Statistical analysis

Overall survival (OS) was calculated from the date of diagnosis to the date of death from any cause. Event-free survival (EFS) was calculated from the date of diagnosis to the date of relapse, death, or disease progression. Analysis was conducted using SPSS version 10 (IBM, NY, USA). Quantitative variables are summarized as mean ± SD; qualitative data are summarized as frequency and percentages. Kaplan-Meier survival estimates and the log-rank test were used to compare survival curves; a p-value ≤0.05 was considered statistically significant. Multivariate analysis was done using the Cox-proportional hazard method.

Results

The 3-year overall survival and event-free survival of the study group were 72% and 68% respectively. The patients' characteristics are illustrated in (Table 1).

Table 1
Demographic characteristics of the study group

		Number (%)
	Total number of patients	68
Age (months)	Mean	27.5 ±39.9
	Median	14
	Range	(1-204)
	Age <36months(3 years)	55 (80.9%)
	Age >36 months(3 years)	13 (19.1%)
Gender	Males	43 (63.2%)
	Females	25 (36.8%)
Initial AFP	<100	4 (5.8%)
	>100	64 (94.1%)
Platelet count	<500,000	14 (20.6%)
	>500,000	54 (79.4%)
Distant metastasis	Non metastatic	54 (79.4%)
	Lung metastasis	13 (19.1%)
	Bone metastasis	1 (1.5%)
Tumor site	Right lobe	41 (58.9%)
	Left lobe	9 (16.4%)
	Both lobes	14 (19.2%)
	Caudate lobe	4 (5.5%)
Focality	Unifocal	57 (84.9%)
	Multifocal	11 (15.1%)
Evans stage	Stage 3	54 (79.4%)
	Stage 4	14 (20.6 %)
PRETEXT Stage	II	32 (47.1%)

	III	30 (44.1%)
	IV	6 (8.8 %)

Surgical resection was feasible in 47/60 patients (78.3%) via partial hepatectomy, ten patients had a log reduction <1 and 37 patients with log reduction>1. Eighteen patients had resection post 2 cycles of chemotherapy, 25 patients post 4 courses of chemotherapy, while only 4 cases underwent resection post 6 courses of treatment. (Figure 1) illustrates outcome of our study group.

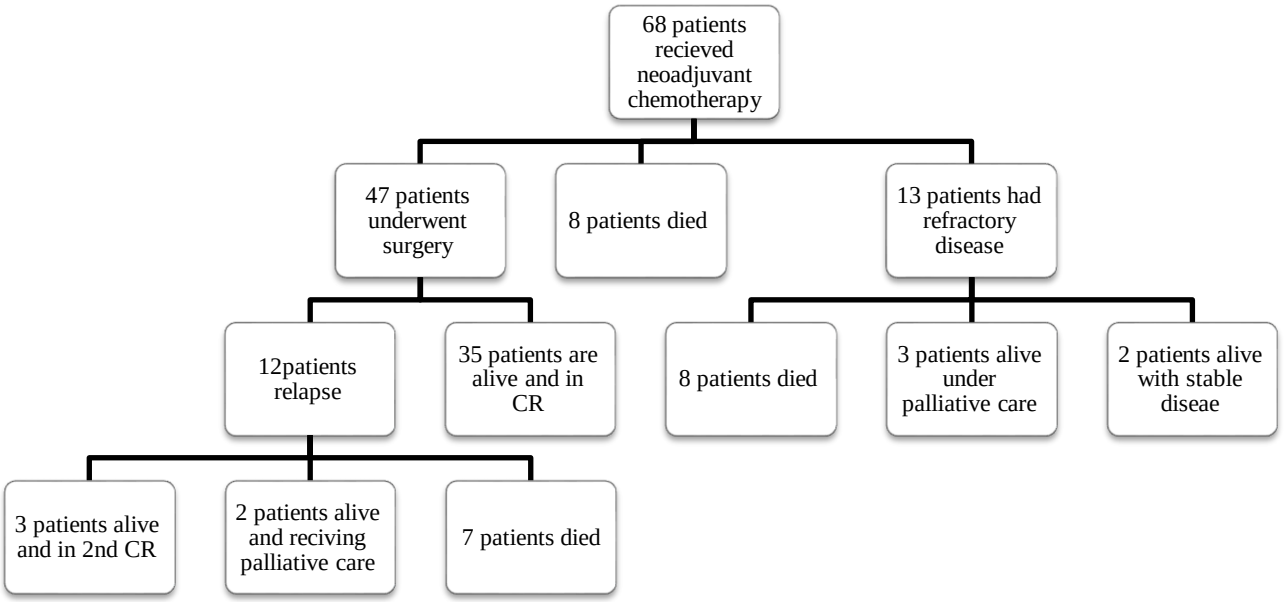

Figure 1: The outcome of studied hepatoblastoma patients

Evaluation (radiological +/- AFP level) using RECIST criteria was done for 61 patients post cycle 2, 58(85.3%) patients showed partial remission, and 3(4.4%) cases had stable disease. We analyzed possible correlations between changes in AFP (after the completion of the first two chemotherapy cycles) and survival outcomes. AFP level was measured post-cycle 2 in 60 patients, (seven that died during the first two chemotherapy cycles, and 1 patient with missing data were excluded); 44 (73.3%) patients showed a decline in AFP level by >1 log reduction. Univariate analysis showed that the 3-year EFS was 75.6% for patients with >1 log reduction in AFP level, compared with 40.1% for those with <1 log reduction (p=0.010). The 3-year OS' for patients with >1 and <1 log reduction in AFP level after the first two chemotherapy courses were 80.4% and 39.4%, respectively (p=0.005).

For the 47 patients who underwent surgical resection the 3-year event-free survival of patients with >1 log reduction in AFP level was 83% compared to those with<1 log reduction and the 3-year DFS of 48% with a statistically significant p-

value of 0.025 (Figure 2&3). AFP log reduction in overall survival and event-free survival.

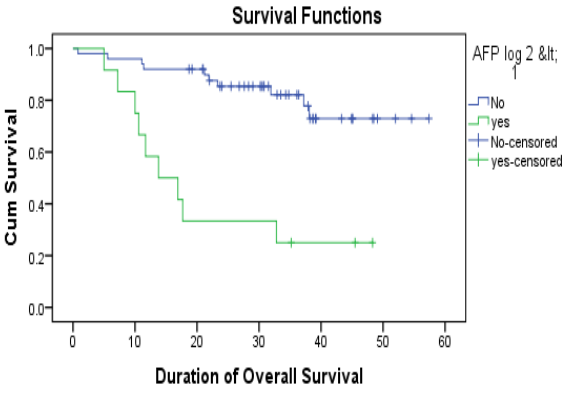

Figure 2: AFP log reduction overall survival.

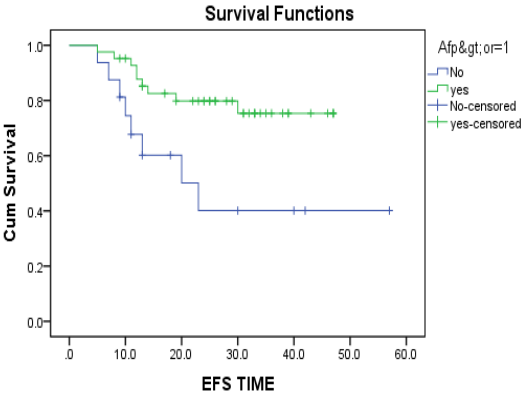

Figure 3: AFP log reduction event-free survival.

On multivariate analysis; Patients with AFP log reduction< 1 had worse OS/EFS compared to those with log reduction>1 with hazards ratio (HR): 3.9 and 95% confidence interval (CI):1.4-11.2, p value=0.011 and HR: 3.2 and 95% CI: 1.3-8.9, p value=0.013 respectively. (Table 2) illustrates the survival outcome of our patients.

Table 2
The survival outcome and its correlation with different prognostic factors

		No. of patients	cum. OS at 36months	p-value	cum. EFS at 36 months	p-value
Whole group		68	67.3%		60.9%	
Gender	Males	43	73.2%	0.547	72%	
	Females	25	63.2%		65.7%	0.643
Age	<3years	55	69.8%	0.052	68%	
	>3years	13	37.5%		16.7%	0.013
Tumor site	Right lobe	41	70.7%		65.7%	
	Left lobe	9	88.9%	0.046	67.9%	
	Both	18	54.5%		45.3%	0.102
PRETEXT stage	II	32	81.3%	0.012	76.5%	
	III&IV	36	56.9%		47%	0.034
Focality	Unifocal	57	76.3%	0.003	68.2%	
	Multifocal	11	27.7%		20.8%	0.005
Metastasis	No	54	78.1%	0.025	65.8%	
	Yes	14	40%		40.2%	0.074
Initial AFP	<100	4	25%	No p-value	25%	No p-value
	>100	64	71.8%		61.5%	
AFP log post cycle 2	<1	16	39.4%		36.5%	
	>1	44	80.4%	0.005	75.4%	0.004

Discussion

Over the past two decades, multicenter cooperative study protocols for the treatment of children with HBL have been developed in studies conducted in the United States, Europe, and Japan. The data from these studies have resulted in improved outcomes for patients with HBL based on the use of a combination of surgical resection and Chemotherapy [6]. Cisplatin-based pre-and postoperative chemotherapy has contributed substantially to the marked improvement in the prognosis of patients with hepatoblastoma [4]. Initial AFP concentration and its decline after neoadjuvant chemotherapy are considered as having a strong prognostic value [7,8,9].

In our study, we identified only 4 patients with a low AFP concentration (<100) at diagnosis and all of them were with small cell undifferentiated (SCU) pathology subtype, their 3 years OFS and EFS were low at 25%. Only 2 cases underwent surgical resection yet this was not statistically significant this could be attributed to the small number of cases.
In an analysis of SIOPEL trials results covering the years of 1995–2006 (including 541 patients with hepatoblastoma), low initial AFP levels below 100 was an independent prognostic factor for poor survival with an EFS 49% [10]. This was also reported in the German HB 94 trial where the differences in the outcome of the 7 children with initial α-fetoprotein levels < 100 ng/mL showed 3 years DFS rate of 43% and the other 61 children; with a DFS rate 87%) was significant (P = 0.0005) [11]. The COG trial INT 0098 results showed that the presence of either AFP < 100 at diagnosis or SCU elements were statistically significant predictors of increased risk of death (p-value 0.0007) [8].

The rate of decline in AFP level post 1st 2 courses of chemotherapy by more than 90% was associated with better survival outcomes and these patients had a 3-year OS&EFS of 80.4% and 75.4% respectively. The use of the 90% decline (1 log10) as a marker of therapeutic efficacy was based on many other articles' results, which used the decline in AFP levels as a prognostic marker [12,13,14].

One study conducted at St Jude hospital over stage 3 and 4 hepatoblastoma showed that After the first two chemotherapy courses, 24 (71%) of 34 patients had AFP decline of ≥90%(>1 log reduction) and for those patients, the 5-years EFS and OS were 92% and 96%, respectively. These outcomes were significantly better than for the patients with AFP levels who showed <90% decline, whose 5 years OS/EFS were 50% and 43% respectively [13].

In another study conducted in Japan over 14 patients of HB demonstrated that none of the patients whose AFP log reduction>1 experienced relapse [15]. However, in the recent COG trial AHEP0731 for the high-risk HBL patients, the AFP decline following the first two cycles of VI (vincristine/irinotecan) was not predictive of outcome probably due to the small number of the patients [14]. The ease of AFP determination makes it a tool that could be used routinely to evaluate therapeutic efficacy, assess the early response of treatment to identify the group of patients who are poor responders to chemotherapy, and tailor our treatment accordingly.

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Data availability: The data that supports the findings of this study are available upon reasonable request from the corresponding author. The data are not publicly available due to the containing information could compromise the privacy of research participants.

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