ASSESSMENT OF ALPHA-FETOPROTEIN CHANGE IN HEPATOBLASTOMA TREATMENT IN CHILDREN

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ABSTRACT

Objective: *To evaluate the change of Alpha – Fetoprotein (AFP) levelsin the therapy process, in order to assess the efficiency of surgery and chemotherapy and a prognosis factor in children's hepatoblastoma treatment.*

Methods: *Pre- respective study. This study focuses on 31 children hospitalized in Pediatric Hospital I, II from January 2002 to April 2014, who were operated on and received chemotherapeutic treated post-op. followed by the same research pattern.*

Results: *There were two groups: the survivors and the fatalities. In the survivor group, the difference of AFP level only appeared in cyacle 2, 3 with $p<0.05$, and had a special meaning in cycle 4 with $p = 0.000$. In this group, the AFP level decreased very quickly from cycle 1 to cycle 2, went down to normal digit at cycle 3and oscillatedaround the normal digit after 4 cycles.In the death group,the AFP level decreased at first, but it quickly increased at the end of the last cycle.*

Conclusion: *The AFP level is much higher than 20ng/ml in all hepatoblastom children. Increasing the AFP level about ≥ 2logs or decreasing ≤ ten squared is a good prognosis in hepatoblastoma treatment process. The changing of AFP level help us to assess good efficiency or discover local relapsedtumorsor lung metastases.*

Key words: *Alpha – Fetoprotein (AFP), chemotherapy, surgery, cycle.*

I. BACKGROUND

AFP is a_1– glycoprotein, produced initially from fetal yolksac, then liver cells and then gastrointestinal tract. AFP disintegrates in 5 to 7 days. The level of AFP is increasing during the pregnancy period. It reaches its limit from week 12 to week 14 of that period. AFP levels decrease in the following time, to lower than 20mg/ml in mature or a-year-old children [1]. AFP is a biological markerfor prognosis and monitoring during the Hepatoblastoma treatment process.

II. METHOD

Pre- respective study. This study focused on 31 children, hospitalized in Pediatric Hospital I, II from January 2002 to April 2014, were operated on and received chemotherapeutic treated post-op followed by the same research pattern.

III. RESULTS

3.1. AFP level before and after surgery

- AFP level before surgery and 2 weeks later

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Table 1: Compare the AFP level (ng/ml) before the surgery and 2 weeks later

Characteristics	**Median (Quartile)**	***p*** (*)
Before surgery	121,000 (21,000 – 1,397,700)	p <0.001
Two weeks later	10,350 (847 – 35,000)	

(*) *Wilcoxon test*

AFP level decreasedafter two weeks of the surgery compared with its level before with p<0.001, which is a valuable statistic. After 2 weeks of surgery, the median AFP is 10,350. There had been no case with AFP level below 100ng/ml before surgery.

- AFP level before the surgery between two groups: survivor and death

Table 2. Compare the AFP level before the surgeries between the two groups

	Median (Quartile)	***p****
Survivor	78,000 (78,000 – 322,783)	p= 0.03
Death	2,152,600 (121,000 – 8,750,000)	

(*)Mann- Whitney test

There is the valuable statistical difference in the AFP level between the two groups before surgery, p < 0.05.

- AFP level between two groups after surgery 2 weeks later

Table 3. Compare AFP level between two groups after surgery 2 weeks later

	Median (Quartile)	***p****
Survivor	1084 (436 – 35,000)	p= 0.054
Death	35,000 (10,350 – 35,350)	

(*)Mann- Whitney test

There isn't any valuable statistic difference in the AFP level between the two groups after surgery 2 weeks later, p > 0.050.

3.2. AFP level result through each chemotherapeutic cycle

Table 4: AFP level result through each chemotherapeutic cycle (N=29)

AFP	N	**Median** (Quartile)
Cycle 1	29	407 (122 –35,000)
Cycle 2	29	209 (67 – 21,526)
Cycle 3	29	11 (7 - 220)
Cycle 4	28	24 (7 – 70,275)
Cycle 5	18	16 (2 - 113)
Cycle 6	18	18 (6 - 87)

Investigating the AFP median before the surgery and throughout each chemotherapy cycle noticed that it rapidly decreased from 121,000 (before the surgery) to 11 (cycle 3) and 24 (cycle 4). The AFP median mostly decreased in cycle 1 which determines the important role of surgery and chemotherapy. Effective chemotherapy was determined by the decreasing of AFP median after each chemotherapy cycle.

3.3. Investigating the AFP median in the four-primary chemotherapy cycles between two groups: the survivor and the death

Table 5. AFP median in the four-primary chemotherapy cycles between two groups

AFP	Death	Survivor	
	Median (Quartile)	**Median** (Quartile)	*p* (*)
Cycle 1	35,000 (309 – 35,550)	262 (65- 465)	**0. 06**
Cycle 2	35.000 (209 – 584,500)	74 (21- 465)	**0. 02**
Cycle 3	112 (31 – 105,000)	8 **(3 - 64)**	**0. 02**
Cycle 4	105,000 **(35,550 –433,000)**	7 (2 - 54)	**0. 00**

(*)Mann- Whitney test

There wasn't any valuable statistical difference in the AFP levelof cycle 1 between the two groups ($p>0.05$).

There were valuable statistical differences in the AFP levels of cycle 2, cycle 3 and cycle 4 between the two groups ($p < 0.05$).

3.4. AFP medianof a group which survived throughout 6 cycles

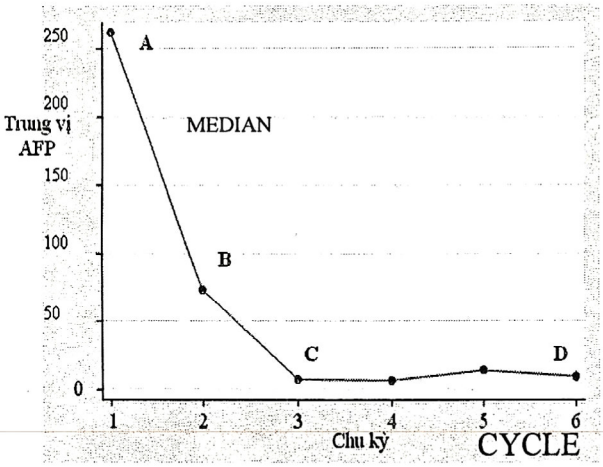

Fig 1. AFP median of a group which survived throughout 6 cycles

Characteristic AFP level of this group decreased to ten squared, and then oscillated around the normal digit (20ng/ml).

The line from A to D describes the AFP level throughout 6 cycles:

- AB segment describes the AFP level decreases very quickly from cycle 1 to cycle 2, but then it doesn't reach its normal digit.
- BC segment describes the AFP levelcontinues decreasing and then goes down to normal digit at cycle 3.
- CD segment describes the AFP level oscillates around the normal digit after 6 cycles

3.5. AFP median in a group that died after cycles

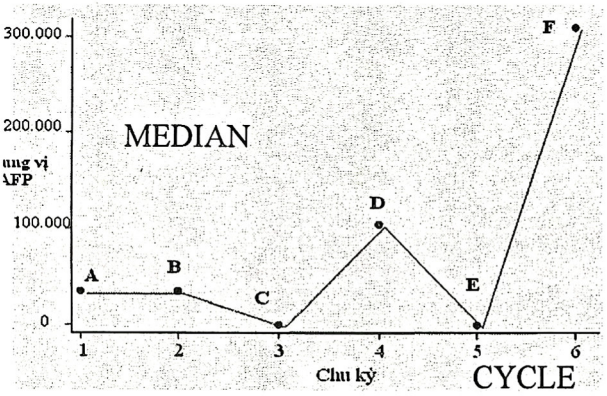

Fig 2. AFP median in a group that died after cycles

The characteristic AFP level in this group is slowly decreasing and suddenly increasing above ten squared.

The line from A to F describes the AFP level through 6 cycles:

AB segment describes the AFP level from cycle 1 to cycle 2 as being stable and above the normal digit.

BC segment describes the AFP levelslowly decreased and returned to a normal digitat cycle 3.

CD segment describes the AFP level rapidly increasing within cycle 4. DE and EF segment describes the AFP level decreasing at first, but it quickly increases at the end of the last cycle.

IV. DISCUSSION

4.1. AFP level before and after surgery

- AFP level before surgery and 2 weeks later

According to table 1, the AFP level before the surgery of all cases highly increased above the normal digit, with 121,000 (Me), but its leveldecreased down to 10,350 two weeks later or after surgery. Comparing the AFP level before the surgery with its effective decline two weeks later determined the excellent result of surgery. The median10,350 which can be explained by Ishak, shows that there is the reminder of microscopic tumor, invased blood wall or some hidden foci metataseswith especially in lung.

According to table 2, the comparison of AFP levels between the two groups before the surgery supplied the difference which is a valuable statistic, p=0.03. Author Von Schweinitz has discovered that the AFP level above 1,000,000ng/ml which contributes to the spread of distal metastases. It is also a prognosis factor in the progress of hepatoblastoma treatment.

In the death group, the AFP level of pre-op increases above 10^6 in the research which involves to the silent spread of the disease. On the other side, AFP level is only 10^3 in the survivor group.

According to table 3, two weeks after operation, there was different data between the two groups that is not valuable statistics. p=0.054. AFP level of

death group was still much higher than the normal although the tumors had been totally removed. It showed that the disease still kept going on or silent metastase. The decline of AFP level in both groups proved that surgery played an important role in BNBG treatment [5], [4].

Feusner and his partners have followed 33 stages - I who were treated by surgery. During that time, there were 10 relapsed cases, including 6 cases with lung metastases [2]. Passmore and his partners represented a case of 12 – year – old boy, whose tumor had been totally removed. Later, this boy was discovered with a lesion in his lung. Feusner and Passmore suggested to pay attention to the role of chemotherapy after the surgery.

4.2. AFP level result through each chemotherapeutic cycle

- AFP median two weeks after the operation and two weeks after the first chemotherapy cycle.

Although the tumor was completely removed, tumor cells can still remain at the margin of the cut or silently move to other parts of the body when AFP medianwas 10.350 after operation. If the AFP level doesn't go back to the normal point, chemotherapy must be done.

Two weeks after surgery, the median of AFP is 10,350 compared to 407, after cycle 1. However, medicinesof chemotherapy can't kill all of the tumor cells because it only affects well on dividing cells. Cells, which are in "silent stage", are not sensitive to chemotherapy.

- AFP median after the cycle 1-2

AFP median after the cycle 1 was 407, and the cycle2 was 209 which showed how effective the chemical medicines were.

After the cycle 2,because of the high AFP level, the cycle 3of chemotherapy was needed.

- AFP median after the cycle 3

AFP median after the cyclewas 11. AFP level has been back to the normal. Surgery combined with chemotherapy has been successful in removed tumor cells produced AFP and sensitive to chemotherapy.

However, the research focused on 10 patients with the AFP level< 220, and it is higher than normal volume. This group was paid attention to in how their bodies responded to the chemotherapy. In this group, there were three of them who had the remainder of tumors at the margin.

- AFP median after the cycle 4

The results of AFP level were almost normal. But, there was a group of ten children with the AFP < 70,275. After the cycle 4, 28 of them survived and continued with the treatment,and one died.

Investigating the AFP level of the one death showed that there was a decline of AFP after surgery but it happened very slowly, and was impossible to go back to the normal range. This patient didn't respond well enough with the treatment and passed away. Von Schweinitz has also noticed the recurrence of the disease in this patient since the cycle 4.

- AFP median after the cycle 5, 6 and 7

AFP levelafter the cycle 5was 16 and cycle 6 was 18. They reached the normal.

After the cycle 4, there were 10 patients who recovered and stopped the treatment.

4.3. AFP median in a group that died after cycles

Table 6. AFP median in a group that died after chemotherapeautic cycles

	Cycle 1	Cycle 2	Cycle 3	Cycle 4
Median	**35,000** (309- 35,550)	**35,000** (209-584,500)	**112** (31-105,000)	**105,000** (35,550-433,000)

The separating time, followed by PLADO schedule, between 2 cycles is 14 days [4], [5] [6]. Comparing the median between cycle 2 and 3, the decline of the AFP level involved with the numerous tumor cells were killed by being sensitive with the medicines.

However, when comparing AFP median of cycle 1 and 2, cycle 3 and 4, there were a group of silent cells

that did not respond to chemotherapy. The moment which the cells set into "silent mode" is the spare moment between 2 cycles.

The AFP median of cycle 2 increased much more than the normal range. There was a possibility to the existance of a mass of malignant cells which resisted the chemotherapy.

In 2007, Warmann exclaimed about the chemical resistance of malignant cells in hepatoblastoma and strongly expressed the important role of completely removing tumors [10].

4.4. AFP median in a survival group after cycles

The AFP median of the survival group had some specific characteristics: stable, decline to the normal range from cycle 3.

Table 7. AFP median in a survival group

	Cycle 1	Cycle 2	Cycle 3	Cycle 4
Median	262 (65-465)	74 (21-465)	8 (3-64)	7 (2-54)

The AFP level of the survival group had decreased from cycle 1 to cycle 4 and below 10ng/ml. These patients responded excellently to the surgery and chemotherapy treatment.

4.5. Comparing the AFP level in each cycle between two survivor and death group

In the survivor group, the difference of AFP level only appeared in cycle2, 3 with $p<0,05$, and had a special meaning in cycle 4 with $p = 0,000$. Chemotherapy had been performed since cycle I, but it didn't reflect the result of the treatment yet. From cycle 2,3 và 4, in the death group, the AFP level is still much higher than ten squared. The chemotherapy didn't continue to totally destroy new cells which resisted chemotherapy.

According to Fig 1, the line of the survival group has showed that the AFP level rapidly decreased, and did not increase since cycle 2,3 and 4. From cycle 3, the AFP level was normal.

The AFP level rapidly decreased from cycle 1,2, returned to normal range in cycle 3 and were stable in the following cycles which had great meaning with the survival times.

4.6. The importance of the AFP level in Hepatoblastoma treatment

In 1997, Van Tornout and his partners investigated the AFP level of 31 patients who were given the second surgery after having been treated with chemotherapy for 4 cycles. When researchers investigated the 4 cycles of chemotherapy treatment, Van Tornout noted the AFP level increased >=1log and specially increased >= 2 logs was an independent factor in treatment [8]. In 2011, Koh and his partners investigated the AFP level of 43 patients. Koh also noted the AFP level decreased >=1log and specially decreased >= 2 logs that related the fail in treament [3].

V. CONCLUSION

The AFP level is much higher than 20ng/ml in all hepatoblastom children. Increasing the AFP level about ≥ 2logs or decreasing ≤ ten squared is a good prognosis in the hepatoblastoma treatment process. The changing of AFP level helps us to assess good-efficiency or discover local relapsedtumorsor lung metastase.

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