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Original Article

SURVIVAL AND TUMOR RELAPSE RATE ACCORDING TO ALPHA-FETOPROTEIN LEVEL IN PATIENTS SUBMITTED TO LIVER TRANSPLANTATION

Correlação do nível de alfa-feto proteína, índice de sobrevida e recidiva tumoral em pacientes submetidos a transplante hepático

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ABSTRACT - ***Background*** - Liver transplantation for hepatocellular carcinoma (HCC) can result in a potential cure and greater survival than other less radical techniques. ***Aim*** - To analyze the survival and recurrence rate in liver transplant recipients with hepatocellular carcinoma and alpha-fetoprotein over 200 ng/ml. ***Method*** - Analysis, in this retrospective study, 90 cirrhotic patients with hepatocellular carcinoma who underwent orthotopic liver transplantation between 1997 and 2009. Liver lesions were diagnosed by preoperative Doppler ultrasonography, abdominal computerized tomography and alpha-fetoprotein blood level. Two groups were studied according to alpha-fetoprotein level over or below 200 ng/ml. The Kaplan-Meier method was used to study survival rate. The Cox regression analysis was performed to study predictive factor to survival. ***Results -*** It was observed that risk of death was 1% for each 10 units of alpha-fetoprotein over 200 ng/ml and 1% for each mm over 28 mm (tumor size). In this sample average age, gender, presence of recidivism, vascular invasion, incidental tumor, Edmondson-Steiner grade and Milan criteria were similar when the two groups were submitted to multivarite analysis and the survival rate and the size of great nodule had a significant difference between the two groups. The survival rate was better for those patients with alpha-fetoprotein<200 ng/ml. ***Conclusion*** - Patients who had alpha-fetoprotein >200 showed worst survival and size of tumor was a predictive risk factor for mortality but this did not have influence in relationship to tumor recurrence.

HEADINGS – Carcinoma, hepatocellular. Liver transplantation. Recurrence. Survivorship.

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RESUMO – ***Racional*** - O transplante hepático para carcinoma hepatocelular pode resultar em potencial cura e melhora da sobrevida comparado com operações conservadoras. ***Objetivo*** - Analisar os índices de recorrência e sobrevida em pacientes transplantados hepáticos por carcinoma hepatocelular e com níveis séricos de alfa-fetoproteína maiores que 200 ng/ml. ***Método*** - Foram analisados retrospectivamente 90 pacientes cirróticos com carcinoma hepatocelular submetidos à transplante hepático ortotópico entre 1997 e 2009. As lesões hepáticas foram diagnosticadas no pré-operatório por ultrassonografia com Doppler, tomografia computadorizada e níveis séricos de alfa-fetoproteína. Os pacientes foram divididos em dois grupos de acordo com o nível de alfa-fetoproteína (menor ou maior que 200 ng/ml. O método de Kaplan-Meier foi usado para calcular a taxa de sobrevida. A análise de regressão Cox estudou os fatores preditivos de sobrevida. ***Resultados*** - Pacientes com alfa-fetoproteína maior que 200 ng/ml (n=6) apresentaram menor taxa de sobrevida em um e cinco anos e na média de meses comparados com o grupo com alfa-fetoproteína menor que 200 ng/ml (n=84); respectivamente 35%, 18% e 11,8 meses contra 68%, 43% e 28,1 meses. Além disso, a taxa de recidiva foi 16,6% no primeiro grupo, e de 5,6% no outro. Observou-se risco de óbito de 1% para cada 10 u de alfa-fetoproteína>200 ng/ml e para cada mm da maior medida de tumor acima de 28 mm. ***Conclusão*** - Os pacientes com valores séricos de alfa-fetoproteína maiores que 200 ng/ml demonstraram menores taxas de sobrevida, porém não foi preditivo de recidiva tumoral.

DESCRITORES - Carcinoma hepatocelular. Transplante de fígado. Recidiva. Sobrevida.

INTRODUCTION

Hepatocellular carcinoma (HCC) is described as the third leading cause of cancer mortality worldwide, accounting for approximately 500,000 deaths per year[11,13]. It is characterized by high incidence in patients with chronic liver disease and causes great epidemiological impact[8,11,13].

Its incidence is increasing annually in Western countries as a result of the increasing number of patients infected with hepatitis C and B. According to epidemiological estimates the incidence tends to increase over the next two decades[2,8,20].

Surgical treatment is currently the best therapy for the treatment of HCC because of tumor recurrence after total liver transplantation (TOF) and has been demonstrated as an appropriate option in the early stages with potential for cure and survival implement[14,20].

The five-year survival in 75% of the cases is similar to patients undergoing liver transplantation without HCC especially in patients who are within the Milan criteria (single nodule <5 cm in diameter or up to three nodules 3 cm indiameter[18].

However, rates of recurrence of HCC after liver transplantation vary from 3.5 to 26% in several studies conducted in large cities and is attracting attention and caution[2,12,14,18,24]. The risk of recurrence was bound to some variables such as nodule size assessment of the explant, histological differentiation, presence of macrovascular invasion, microvascular and preoperative level of alpha-fetal protein (AFP). These variables are currently the best predictors of HCC recurrence after liver transplantation[5,10,23,24].

The serum alpha-fetoprotein, initially described by Abelev, et al.[1] in 1963 is the most widely used tumor marker for screening and monitoring of HCC worldwide. Several studies have shown that high alpha-fetoprotein is a bad prognostic factor regarding aggressiveness of the disease are thus linked, at high levels, the larger diameter tumors and vascular invasion. In these studies, the cutoff value associated with worse prognosis is 200 ng/ml[1,9,16,19].

The aim of this study was to analyze the rate of recurrence and survival in patients undergoing orthotopic liver transplantation for HCC and serum alpha-fetoprotein greater than 200 ng / ml[1,9,16,19,21].

METHOD

It was analyzed 90 cirrhotic patients with a preoperative diagnosis of HCC who underwent liver transplantation at the Clinical Hospital of Campinas,SP, Brazil between January 1997 and September 2009.

The preoperative diagnosis was obtained in accordance with criteria established by the EASL (European Association for the Study of Liver) and AASLD (American Association for the Study of Liver Disease). It was used computerized tomography, Doppler ultrasonography and/or MRI of abdomen showing arterial hypervascularity and serum alpha-fetoprotein[12].

All patients underwent surgical intervention had to be within the Milan criteria for inclusion in the list of pre-transplantation and preoperative evaluation.

During the wait list some patients underwent chemotherapy or selective alcoholysis when necessary, by decision of the multidisciplinary team, according to the stage and tumor location.

Patients in whom diagnosis were outside the Milan criteria were treated for "downstaging" (tumor shrinkage obtained by alternative methods such as therapeutic chemoembolization or ethanol) and subsequently underwent transplantation, following the laws of the country.

After transplantation all patients were monitored by serum alpha-fetoprotein and abdominal ultrasonography every three months to the end of the first year and after every six months until the end of the second year. In cases of suspected recurrence were performed computerized tomography or magnetic resonance imaging of the abdomen.

The assessment of liver function was obtained through the MELD score (Model for End-stage Liver Disease)[6]. Patients transplanted prior to 2005 had their liver function calculated retroactively

The variables were: age (years), gender (male or female), blood levels of alpha-fetoprotein levels above or below 200 ng/ml, tumor size (in mm), number of nodules, histologic second stage Edmondson-Steiner (grade I, II, III), presence of macrovascular and microvascular invasion observed in the explant, or may not be within the discretion of Milan after evaluation of the explant, incidental presence of tumor or may not have had a recurrence or not, survival and tumor recurrence at the end of the first and fifth year.

Statistical analysis was performed using the program Statistica 7.5/2007-Softstat-Chicago/USA. Descriptive analysis was used to observe the frequency and averages. Comparing the groups with and without AFP greater than 200 ng/ml was performed using the Wilcoxon test. The survival including the period between surgery and the last visit was calculated using the estimation method of Kaplan-Meier survival and prognostic factors for recurrence were evaluated using the Cox regression test.

RESULTS

It was evaluated 90 cirrhotic patients transplanted with a preoperative diagnosis of HCC, were 72 male patients (80%) and 18 females (20%). The mean age at transplantation was 52.3 years (33-68 years).

It was found as cause of the liver disease virus C in 54% of patients, followed by alcohol 22%, HBV in 19% and 5% in other causes.

The average follow-up was 42 months, the average levels of alpha-fetoprotein was 42.3 ng/ml and the average size of nodules in its largest diameter was 32 mm. The patients had MELD score results and levels of immunosuppressive drugs similar regardless of the level of AFP.

The preoperative treatment with chemo-embolization for "downstaging" was performed in 13 patients and none of them had tumor recurrence.The recurrence of HCC after transplantation was found in six patients (6.7%) with an average time of nine months between surgery and diagnosis of recurrence.

Although 72% of patients were within the Milan criteria on the observation of the explant, only three (of six with relapsed) patients went beyond these criteria after evaluation of the explanted liver, 39.2% of patients with AFP<200 ng/ml extrapolated these criteria usually due to the number of tumor nodules observed. It was also noted that 2% had macrovascular invasion and 18% microvascular injury not observed in these imaging tests prior to transplantation.

The sites of tumor recurrence were: liver in three patients, lung in one and multiple sites (lung, brain, liver and bones) on another patient.

In all cases the treatment of recurrent change of immunosuppression consisted of calcineurin inhibitor to sirolimus in one patient and was associated with the ᴿSorafenib chemotherapy.

In Table 1 can be observed the average frequency of variables. It was also noted that only six (6.7%) had AFP>200 ng/ml, with no statistical difference in the appearance of recurrence.

TABLE 1 – Characteristics according to the blood level of alpha-fetoprotein (AFP) in patients undergoing liver transplantation for hepatocellular carcinoma

AFP	> 200 ng/ml	< 200 ng/ml
Patients	6 (6,7%)	84(93,3%)
Age (years)	55,3	50,5
Gender (female / male)	1,1% / 83,3%	17,9% / 82,1%
Recurrence (s / n)	16,6% / 83,3 %	5,6% / 94,4%
Vascular invasion (y / n)	16,6% / 83,3%	21,4% / 78,6%
Milan criteria (y / n)	50% / 50%	39,2% / 60,7%
Tumor incidental (y / n)	0 / 100 %	44,0 % / 64,0%
Stage (I / II / III)	0 / 100% / 0	6,0% / 50% / 44%
Nodule size (mm)	31,6 (12-50)	12,3 (1- 60)
1 year survival	35%	68%
Survival 5 years	18%	43%*
Tumor recurrence	16,6%	5,6% (P=0,054)
Average survival (months)	11,8	28,1 *

*= p <0.05, mm=millimeters; S=yes, N=not

Only one patient with a diagnosis of recurrence after transplantation, showed AFP above 200 ng/ml and the mean AFP in these patients was 64.58 ng/ml.

The Cox regression test showed that the level of AFP and tumor size could be considered as an independent risk factor for survival (risk of death for each 1% 10u AFP above 200 ng/ml - p=0.002, HR=0.0178 - 95%=0.0096 to 0.356) and 1% mortality risk for each mm above 28 mm tumor (p=0.04, HR=0.0169 - 0.0094=95% - 0.299) (Figure 1)

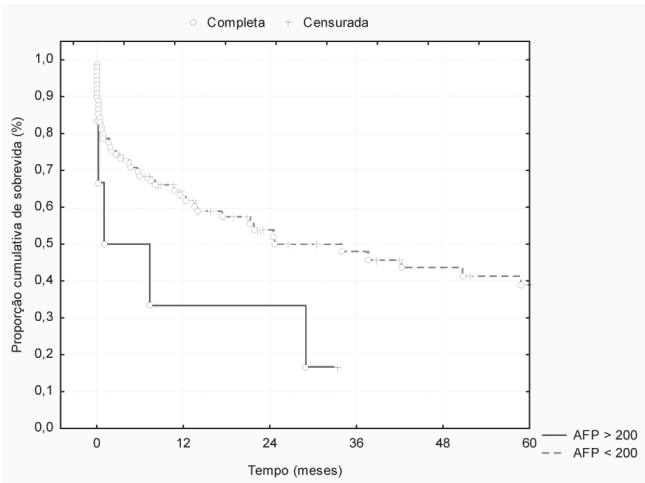

FIGURE 1 – Cumulative survival in patients undergoing liver transplantation for hepatocellular carcinoma according to the level of alpha-fetoprotein (AFP) higher or lower than 200 ng/l

DISCUSSION

Alpha-fetoprotein is characterized by being a fetal glycoprotein associated with tumor growth. Physiologically it is a protein synthesized and secreted by hepatocytes, fetal cells in the gastrointestinal tract and germ cells, its serum level decreases gradually after birth until the first year of life while remaining stable normally below 10 ng/ml[1,9,16,19,21]. It has been used widely in the literature as a tumor marker for approximately 40 years, consolidating the participation of this marker in the regulation of oncogenes and growth, with evidence of its role in growth of hepatocytes[1,9,16,19,21]. Hepatocellular carcinoma with high level of AFP has been characterized by increased cellular proliferative activity measured by Ki-67[1,9,16,19,21].

However, recent studies have defined the AFP as a marker gradually with poor specificity and sensitivity rates approximate 60% sensitivity and 70% specificity raising efforts in several different centers in search of better markers[4,12,17,22]. The reason for the low sensitivity and specificity has been attributed to the advancement of imaging methods that today can diagnose smaller tumors, which found in the past usually associated with AFP levels within the normal range[9,16].

In a study of 170 patients diagnosed with HCC,

Trevisani, et al.[25] demonstrated, even establishing a cutoff value of AFP of 200 ng/ml noted for being the best value in the aforementioned study, sensitivity was below 60%, which means 40% of false negatives[25].

In the absence of malignancy, the level of AFP may appear high in cases of replication by hepatitis B and C[7,15], these agents commonly related to chronic liver disease predisposing to the development of HCC which can often hamper the specificity of method.

Furthermore, the level of AFP may also appear high in gastrointestinal tumors than HCC, such as cholangiocarcinoma. This fact has great relevance since the treatment and prognosis of cholangiocarcinoma presents the different HCC especially with regard to the indication for liver transplantation[7]. The indication for liver transplantation for cirrhotic patients with a diagnosis of HCC has been presented as a good therapeutic alternative, with similar survival to transplantation performed for other causes[2,14,18,20]. However, the rate of recurrence after transplantation varies from 3.5% to 26% in some studies[4,5,10,12,14,23,24] and has raised the need for predictive methods of worse recurrence.The recurrence rate obtained here was 5.6%, consistent with the literature[3,6,12].

Among the variables linked to worsening of the recurrence rate was given major emphasis to alpha-fetoprotein. For this reason, a court of alpha-fetoprotein of 200 ng/ml according to the literature proves to be a negative prognostic factor[1,3,9,16,19,21].

This study, with patients divided into two groups, AFP above 200 ng/ml and AFP <200 ng/ml confirms this finding, in which patients in the first group have a lower overall survival and shorter survival in the first and fifth years post-transplant.

In this study, assessing factors already established in the literature as having the worst prognosis and disease stage, cell differentiation, vascular invasion, Milan criteria and the presence of incidental tumor[5,10,23,24], there was no statistical difference between the groups with higher or lower AFP than 200 ng/ml except for the size of the nodule with its largest diameter.

The association with larger diameter may be associated with the characteristic of promoting greater cellular activity of AFP, however, did not correlate with increased grade of cellular differentiation[1,9,16,19,21].

There was also no statistical difference between the two groups in relation to tumor recurrence, one patient presented with recurrent AFP above 200 ng/nl, leading to corroborate the literature in finding new methods more specific and sensitive for predicting recurrence[4,5,7,10,12,15,17,22,23,24,25]. Observed death risk of 1% for every 10 u alpha-fetoprotein> 200 ng/mL mm and each of the larger extent of tumor above 28mm.

The alpha-fetoprotein above 200 ng/ml was observed in only 6.7% of patients showing poor accuracy in diagnosis, as endorsed by various authors[4,7,12,15,17,22,25].

CONCLUSION

Risk factors associated with worse prognosis were tumor size and AFP. The level of AFP shown to be an insecure and new tumor biomarkers should be investigated.

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