Prognosis of hepatocellular carcinoma in Egyptian patients after living donor liver transplantation (LDLT)

Thesis

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the ten most common cancers worldwide ***(Comar and Clark, 2005) .*** It is also the fifth among men and eighth among women; it is the second among cancers of the digestive tract after stomach cancer ***(Sangiovanni et al., 2004)***.

The estimated annual number of cases exceeds 500,000 **,** with a mean annual incidence of around 3-4% ***(Llovet and Beaugrand, 2003).***

In Egypt, about 7.2% of chronic liver disease patients develop HCC. The development of HCC is mainly due to the high rate of hepatitis B and C infections among Egyptian patients ***(El Zayadi et al., 2005)***.

According to the data from ***National Institute of Cancer***, ***(2007)***, Gharbiah is the first Egypt population based cancer registry. Liver cancer is the second most frequency for males after urinary bladder cancer. It constitutes 13% of all cases. For females, it is the forth after breast cancer, non hodgkin's lymphoma and leukemia constituting 4.1%of all cases.

The number of deaths per year from HCC exceeds 250,000, placing it as the sixth cause of death from cancer worldwide ***(Steel et al., 2004)***.

World-wide, hepatitis B and C are the most important factors for the development of hepatocellular cancer. Co-factors contribute. However, in low prevalence areas, other factors are concerned. The mechanisms in such cases and in particular the role of cirrhosis per se remain obscure ***(Sherlock and Dooley, 2002)***.

Although the prevalence of HCV is declining in developed countries because of the decline in incidence in the 90s, the number of persons with HCC is expected to increase substantially before peaking in 2015 ***(Armstrong et al., 2000)***.

Patients with advanced liver disease, particularly cirhrosis, are those at risk for HCC and should be screened every six months for its development. The risk of developing for a patient with HCV-related cirrhosis is approximately 2-6% per year ***(Sangiovanni et al., 2004).***

Patients with chronic hepatitis B virus infection are known to be at risk for HCC even without cirrhosis, so all patients with chronic HBV (those who are HBsAg +ve) should be considered for screening for HCC ***(Lok et al., 2001).***

In patients with HCV, only those with advanced liver disease (particularly liver cirrhosis) are at risk for HCC so screening should be applied only to these patients ***(Ryder, 2003).***

In Mediteranean countries, HCC develops on diseased liver, which represents the most important risk factor. Therefore, the number of cases is likely to undergo a further increase in coming years because of the spread of the hepatitis C virus ***(Bruix and Llovet, 2002).***

The clinical manifestations of HCC often overlaps with that of cirrhosis, therefore it is commonly diagnosed at asymptomatic phase by routine ultrasound tomography or because of a sudden worsening of underlying cirrhosis ***(Sherlock and Dooley, 2002).***

Surgical resection may be curative if HCC is detected at an early stage. Patients who are <65 years of age,

have Child-Pugh Class A cirrhosis, and have only 1 or 2 tumors are the best candidates for hepatic resection. However, the rate of recurrence of HCC after resection is very high, approaching 25% per year. Moreover, less than 20% of HCC patients are good candidates for surgical resection ***(Mor et al., 1998)***.

Liver transplantation is an accepted therapeutic option for patients with early HCC ***(Pichlmayr et al., 1994).***

Mazzaferro et al. (1996) showed that liver transplantation for early HCC characterized by no major vessel invasion, a single tumor less than 5 cm in size, three or fewer tumors with the largest tumor less than 3 cm in size resulted in a good prognosis. These features are referred to as the ***Milan criteria*** and are now widely accepted to identify suitable candidates for liver transplantation.

Some authors suggested that Milan criteria carries the risk of a significant number of patients who potentially being curative by transplantation being refused from candidate of transplantation, and patients who assumed to be good transplant candidates can be actually at high risk of tumor recurrence ***(Roayaie et al., 2002 and Cillo et al., 2004).***

Several investigators have reported variable expanded criteria for liver transplantation. According to the University of California, San Francisco protocol, the eligibility criteria for down-staging included one lesion ≤ 6.5 cm, two or three lesions each ≤ 5 cm with total tumor diameter ≤ 8 cm, or four or five lesions each ≤ 3 cm with total tumor diameter ≤ 8 cm. These features are referred to as ***extended Milan criteria (Yao, 2006)***.

Kyung et al., (2007) showed that the beyond-Milan patient who did not have preoperative vascular invasion had a 1- and 3-year survival rate of 84.2 and 67.4% respectively.

Other prognostic factors other than tumor size and number were introduced by many authors, for example, pre transplant serum AFP levels were shown to be an independent risk factor for patient survival ***(Jonas et al., 2001)***. In addition, the grade of histological differentiation of the HCC correlated with tumor characteristics and recurrence ***(Furukawa et al., 2006).***

Cillo et al. (2004) reported that survival rates of patients with histological grade 1 and 2 HCC is comparable with patients transplanted for benign disease and that tumor differentiation may accurately reflect tumor aggressiveness and the consequent post transplant risk of recurrence.

With proposed expansion of criteria for transplantation of HCC and long waiting times, ablative therapies prior to transplantation have been widely used. Potential advantages include reducing dropout rates on the waiting list, reducing recurrence rates after transplantation and possibly down staging larger tumors to within Milan criteria before transplantation. The commonly used modalities of HCC ablation include Trans arterial chemoembolization (TACE), radiofrequency ablation (RFA) and percutaneous ethanol ablation (PEI) or cryoablation ***(Schwartz et al., 2007).***

AIM OF THE WORK

The aim of this work is to evaluate the different prognostic factors of liver transplantation among patients with HCC and to compare between Milan and extended Milan criteria in the decision making for liver transplantation.

PATIENTS AND METHODS

This study will be conducted between Tropical Medicine department, Faculty of Medicine, Ain Shams University, Ain Shams Center for organs transplantation (ASCOT) ,Wady El Neel hospital and Egypt Air hospital.

It will include 30 patients diagnosed as HCC and schedeuled for LDLT either according to Milan or extended Milan criteria. All patients will be followed up for at least 1 year to determine the different prognostic factors, recurrence of HCC and 1 year survival rate.

Patients who underwent transplantation according to Milan or extended Milan criteria will be followed by multiple clinical, laboratory and imaging studies, liver biopsies will be performed whenever needed to determine the prevalence of complications. Morbidity and survival will be recorded. The statistical significance will then be determined.

The following studies will be done:

I) Recipient evaluation :

A) Full history and physical examination

B) Lab investigations:

1. ABO blood grouping, Rh.

2. Complete blood picture (CBC) , Erythrocyte sedimentation rate (ESR) and C reactive protein (CRP).
3. Liver profile: total Bilirubin, direct bilirubin, AST, ALT, Albumin, total protein, alkaline phosphates and GGT.
4. Renal profile: creatinine, urea, uric acid, Na, K, CL, PO_4 and Ca.
5. Bleeding profile: PT, PTT, INR, protein C & S, Factor V and prothrombin concentration.
6. Lipid Profile: LDL, cholesterol and triglycerides.
7. Fasting blood sugar.
8. Serum amylase.
9. Copper, Iron profile.
10. Schistosoma Ab titer and/or schistosoma Ag test.
11. Viral markers:
    a. HCV Ab and HCV PCR
    b. HBs Ab , HBs Ag, HBc IgG ,HBc IgM, HBe Ab, HBe Ag and HBV PCR.
    c. HAV IgM.
    d. CMV Ab (IgG –IgM).
    e. EBV Ab (IgG – IgM).
    f. Herpes simplex virus (HSV) (IgG – IgM).
    g. Varicella Zoster virus (VZ) (IgG – IgM).
    h. Human immunodeficiency virus (HIV) Ab
12. Tumor markers: AFP, CEA, CA 19-9, CA 125 in females, CA 15-3 and PSA in males above 50 years.
13. Immunology: ANA, ASM, AMA and LK Ab.

14. Stool analysis.

C) Imaging studies:

1. Chest X-ray.

2. Abdominal US Duplex.

3. Mammography (in Females above 40 years).

4. Spiral CT scan triphasic Abdomen + CT scan Venography.

5. CT scan Chest.

6. Bone scan.

D) Endoscopy:

1. Upper GI endoscopy.

2. Colonoscopy + Rectal snip if Sch Ab titer +ve.

E) Consultations:

1. Cardiac assessment: ECG, Echocardiography and stress Echo for all recipients.

2. Chest assessment including pulmonary functions test .

3. ENT clearance.

4. Dental Clearance.

5. Gynecology clearance and PAP smear (for all female recipients).

6. Psychiatric consultation.

7. Anesthesia consultation.

F) Histopathological examination:

Including number of focal lesions,total tumor volume, histologic grading system was according to ***Edmondson and Steiner (1954)*** and the presense or absence of vascular invasion.

II) Donor Evaluation :

All related Donors are accepted. Recipients who could not find an appropriate related Donor within their families and present with unrelated donor; will be evaluated after approval of the local ethical committee.

Pre-transplant work up:

A)Complete and thorough clinical evaluation to insure the following points:

1. ABO compatible with the recipient.
2. Age between 18-45.
3. BMI < 28.
4. No previous history of major upper abdominal operations.
5. Free from any chronic medical conditions (no history of cardiopulmonary, renal or neurological disease).
6. Psychologically stable.
7. Non smoker, nor drug or alcohol abuser.
8. Female donors should not be pregnant or on hormonal therapy.
9. No evidence of liver abnormalities.

10. No previous liver surgery with the exception of cholecystectomy.

11. No history of diabetes.

12. Hypertension is permissible if mild and well controlled on medications.

13. No history of Deep Vein Thrombosis or pulmonary embolism.

14. No history of bleeding tendencies.

B) Lab investigations:.

1. ABO blood grouping, Rh .

2. Complete blood picture (CBC) , Erythrocyte sedimentation rate (ESR) and C reactive protein (CRP).

3. Liver profile: Total Bilirubin, Direct bilirubin, AST, ALT, Albumin, Total protein, alkaline phosphates and GGT.

4. Renal profile: creatinine, urea, uric acid, Na, K, CL, PO_4 , Ca.

5. Bleeding profile: PT, PTT, INR, protein C & S, factor V and prothrombin concentration.

6. Lipid profile: LDL, cholesterol and triglycerides.

7. Fasting blood sugar.

8. Serum iron and ferritin.

9. Schistosoma Ab titer and/or schistosoma Ag test.

10. Virological workup:

a. HCV Ab – HCV PCR.

b. HBV s Ab , Ag, HBc IgG, HBc IgM Ab, HBe Ab, HBe Ag, and HBV PCR.

c. HAV IgM.

d. CMV Ab (IgG –IgM).

e. EBV Ab (IgG – IgM).

f. Herpes simplex (HSV) (IgG – IgM).

g. Varicella Zoster virus (VZ) (IgG – IgM).

h. Human immunodeficiency virus (HIV) Ab.

11. Tumor markers: AFP,CEA, CA 19-9, CA 125 in females,CA 15-3 and PSA in males above 40 years.

12. Complete Urine analysis including screening for drug abuse: cocaine, opiates, benzodiazepine, cannabinoids, barbiturates.

13. Stool analysis.

C) Imaging studies:

1. Chest X-ray.

2. Abdominal ultrasonography and dupplex.

3. Triphasic CT scan abdomen + CT angio of hepatic vessels + CT Venogram.

4. CT scan Volumetry:

a. GRWR (graft recepient weight ratio): should be at least 0.8 %

b. Remaining liver volume left for the donor at least 30 % of total liver volume.

5. Magnetic Resonance Cholangio Pancreatography.

D) Consultations:

1. Cardiac assessment: ECG, Echocardiography.

2. Chest assessment: including pulmonary functions test .

3. Psychiatric consultation.

4. Anesthesia consultation.

E) Liver biopsy:

1. No liver pathology.

2. Macro-steatosis < 15 %

III) Post operative follow up For recipients:

1. Eelectrolytes: Na, K, Ca, I, Mg, PO4

2. Blood urea, creatinine, creatinine clearance

3. Liver profile: AST, ALT, bilirubin (total and direct), total protein, albumin, GGT, PT.

4. Serum amylase.

5. Fasting blood sugar.

6. Complete blood picture.

7. Coagulation profile: PTT, factor V, fibrinogen, FDP's.

8. Lactic acid.

9. F K 506 (Prograf): trough level.

10. Cyclosporine (Neural): trough level.

11. Abdominal ultrasonography Dupplex.

12. Frequency of follow up:

- 1st week: once / day.
- 2nd and 3rd weeks: 3 times / week.
- 4th week: twice / week.

IV) Long term follow up protocol during 1st year:

1. Eelectrolytes: Na, K, Ca, Mg, PO4

2. Blood urea, creatinine, creatinine clearance

3. Liver profile: AST, ALT, bilirubin (total and direct), total protein, albumin, alkaline phosphatase and GGT.

4. Fasting blood sugar.

5. Complete blood picture.

6. Coagulation profile: PT, PTT, factor V, fibrinogen, FDP's.

7. FK 506 (Prograf): trough level.

8. Abdominal ultrasonography Dupplex at 1, 3, 6, 12 months.

9. Alfa fetoprotein level at at 1, 3, 6, 12 months.

<u>Frequency of follow up:</u>

- 1st 3 months: follow up weekly.
- 3 – 6 months: follow up every 2 weeks.
- 6 – 12 months: follow up every 1 month.

RESULTS

Statistical analysis:

Data will be collected, tabulated, coded then, analysed by a computer software SPSS version 12.0.

Numerical variables will be examined for normality then, will be expressed as mean (standard deviation) or median (interquartial range), whenever appropriate.

On the other hand, categorical variables will be presented as number of cases (percent).

Between groups, comparaison of numerical variables will be performed by paired t tset, unpaired t test (student's test) if they show normal distribution, otherwise, Mann Whitney test will be used instead. Also, Pearson correlation test will be used.

Between groups, comparaison of categorical variables will be performed by Chi-Square test.

A difference in variables will be expressed by P value (> 0.05 is non significant, < 0.05 is significant, and < 0.01 is highly significant).