

Sequential Liver Transplantation

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FAMILIAL amyloidotic polyneuropathy (FAP) is an inherited autosomal dominant systemic disease caused by an abnormal protein—the Transthyretin Methionine 30 (TTR Met 30, in the Portuguese variety—methionine instead of valine). This abnormality is caused by a mutant gene in the 18th chromosome pair, and the main site of production of the TTR Met 30 is the liver (more than 90%). There are a good number of mutants. The largest affected populations are located in Portugal, Sweden, and Japan. The disease becomes clinically apparent in the third decade (for the Portuguese variety) and inevitably progresses to death in 10 to 14 years.^{1,2,3}

Liver transplantation (LTx) drastically reduces the serum levels of the abnormal protein in a permanent way. Thus, it is expected that LTx stops the progression of the disease and, actually, it seems the most promising therapy. Since the first experience by Holmgren, in 1990, almost 200 cases of FAP patients have been transplanted worldwide. Stabilization of the disease and regression of some symptoms have been repeatedly reported.^{4,5} Besides the production of the abnormal protein, no other liver functional disturbance is known and the liver of these patients is anatomically normal. This makes hepatectomy easier than the same procedure with anatomically diseased livers. Given the organ shortage, the use of these livers adequately harvested for implantation in other patients is appealing.

RATIONALE

The logical basis for the use of FAP livers for transplantation in other patients are multiple: the livers are anatomically normal and show no other functional abnormalities than the TTR Met 30 production; the hepatectomy affords liver grafts in the best conditions; the disease requires at least 20 years to develop symptoms in the genetically affected individuals; and it is expected that the TTR Met 30 producing grafts in genetically non-affected patients will need at least the same time to develop symptoms or, more optimistically, will never generate the disease. The most obvious candidates for this sequential or “domino” liver transplantation (SLTx, DLTx) are (at least at the moment), patients with hepato-carcinoma or metastatic disease confined to the liver, not adequate for surgical resection and not accepted in the overloaded waiting lists.

MATERIALS, METHODS AND RESULTS

After full agreement of the Ethical Committee of the HUC, we started DLTx strategy in October 1995. Till now, four advanced oncological patients have received 4 FAP livers retrieved from 4 female adult patients who received 4 cadaver liver grafts. The recipients of the FAP livers were 4 males, 56, 51, 44, and 48 years old, respectively with isolated hepatic metastasis of a resected carcinoma of the sigmoid, hepatocellular carcinoma associated to posthepatitis C cirrhosis, primary hepatocellular carcinoma and, a last patient, with isolated liver metastasis from a previously excised pancreatic neuroendocrine carcinoma. Patient 1 was treated with systemic and intrarterial chemotherapy before transplantation, patient 2 received 3 courses of doxorubicine post-transplantation, patient 3 had been treated with intrarterial chemoembolization, and patient 4 had received systemic chemotherapy for several months in another country. The work-up of all patients included abdominal, thoracic, and cranial CT scans, NMR, angiographies, and exploratory laparotomies with lymph node biopsies.

The main points of the hepatectomy technique in the FAP patients for these SLTx were: use of the external veno-venous by-pass with bio-pump; dissection of the supra-hepatic vena cava above the diaphragmatic fibrotic ring which was divided; dissection of the main hepatic bile duct and hepatic artery limited to a minimum; division of the hepatic artery at the emergence of the gastroduodenal artery; division of the vena porta half a centimeter beneath its bifurcation.

The orthotopic implantation of the FAP liver grafts in the oncological recipients followed the classical technique (with external veno-venous by-pass) in patients 1 and 3 a “piggy-back” variant in the others (without veno-venous by-pass). No particularly important technical difficulties were raised. Only in patient 3 was there a relevant complication: stenosis of the arterial anastomosis favored by a severe periaortic inflammatory reaction secondary to chemoembolization which caused complete thrombosis of the distal celiac trunk. Successful rearterialization of the liver was attained

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through the right renal artery, the kidney being autotransplanted. In patient 2, the supra-hepatic vena-cava was too short and had to be reconstructed before the anastomosis. Patient 4 developed a biliary leakage which was surgically repaired. All patients show very good general condition and normal liver function at 10, 9, 3, and 2 months posttransplantation. Patient 1 alfa-feto-protein increased quite recently and a lung metastasis has been detected. All the F.A.P. donors had a normal evolution post-OLTx.

DISCUSSION

The shortage of cadaveric organs for transplantation has led to important developments in this field, the use of reduced liver grafts, and segmental living donor grafts being the most remarkable. FAP is a progressive incapacitating disease leading to death during the normally most active period of life. The only highly promising therapy, at the moment, is liver transplantation. The hope that this treatment generated rapidly spread among the more than one thousand patients who, only in Portugal, may be suitable candidates for aL Tx. Through diligent procurement and fair allocation of cadaver grafts we estimate that about 50 FAP patients per year may be transplanted in Portugal. This means an additional pool of 50 liver grafts, anatomically normal and also functionally normal, except for the production of the abnormal protein, capable of causing the systemic amyloidosis. However, the minimum time for this disease to show its first symptoms, in the genetically affected patient is at least 20 years and it usually courses to death in a 10- to 14-year period. Whether it will follow the same course in a nongenetically affected person is not known.

The observation that the deposits of the TTR Met 30 in the nerves may not be the primary cause for this amyloidosis provides some support for more optimistic view over the future of the non-genetically individual receiving liver grafts from FAP patients.^{6,7} Whatever the case, the use of FAP livers as grafts for some oncological patients with a short life expectancy seemed to us an ethically acceptable option. Those candidates should have malignancies confined to the livers and not amenable to surgical resection and life expectancy independent of the malignancy should be less than 30 years, this is the minimum total time for the disease to develop and to cause death in the genetically

affected patients. Our four transplanted patients would not be accepted in any national list for LTx. These criteria for inclusion were fully accepted by the independent Ethical Committee of the HUC and supported by specialized legal advise. All patients (both FAP's and oncological recipients) received detailed informations about the procedures. The main principle presiding to this experience regarded the safety of the procedures in the FAP patients, so that no additional risk should be imposed on them by this strategy.

The biochemical and clinical consequences of the use of these livers must wait a long time while expecting that some of these patients live long enough. The immediate hepatic function had been very good as well as the recovery of all 4 patients till now submitted to this transplant. The TTR Met 30 appeared almost immediately in their blood and so it may become a trustful marker of the initial liver function of the transplant. In the future, new insights on the pathogenesis of FAP may come out of this strategy.

In summary, DLTx using FAP patients' livers is an ethically sound strategy that may afford opportunities to transplant some patients otherwise without access to this therapy. It has been a safe procedure for the FAP donors without complications ascribable to specific technical problems. All FAP liver grafts showed very good immediate function. None of these patients has shown any symptoms of FAP despite the quick appearance of TTR Met 30 in their blood after DLTx.

An extended follow-up of the long-term survivals is required to get some answers for the questions raised by this new strategy.

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