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SUMMER SCHOOL: PEDIATRIC HEPATOLOGY

Liver transplantation and liver cell transplantation

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Summary Liver transplantation is nowadays the recognized treatment of many liver diseases and liver-based metabolic disorders in childhood. The indications are congenital cholestatic diseases, mainly biliary atresia, metabolic disorders and fulminant hepatic failure. Potential candidates have to be evaluated early in a specialized center, as the survival rate is worse if the child is transplanted with end-stage liver failure. The graft is in most cases partial, either a split liver from a deceased donor (the other part going to an adult recipient), or the left lobe or left liver from a living donor. The patient's survival rate is about 80—90% at 1 year, 70—80% at 10 years, and the graft survival rate 60—70% at 10 years. Immuno-suppression depends on a calcineurin inhibitor (cyclosporin or tacrolimus), and either steroids or an induction with a monoclonal antibody against IL2-receptor. Early surgical complications are a non-function of the graft (rare), arterial or portal thrombosis, biliary problems (more frequent with partial grafts), bleeding. Infections with bacteria and fungi are frequent and often severe. CMV infection is prevented, or screened and preemptively treated. EBV infection is frequent and may induce a posttransplant lymphoproliferative disease, that can develop into a lymphoma. Early stages are treated with reduction of immuno-suppression and monoclonal antibodies against CD20. Acute rejection is frequent but usually easily controlled. Chronic rejection may be due to poor compliance. Late graft loss is due to chronic rejection or long-standing biliary complications. Long-term complications are progressive graft fibrosis, renal failure due to drug toxicity (mainly calcineurin inhibitors), and cancers (skin and lymphoma).

Keypoints

- Liver transplantation is nowadays the recognized treatment of many liver diseases and liver-based metabolic disorders in childhood.
- The indications are congenital cholestatic diseases, mainly biliary atresia, metabolic disorders and fulminant hepatic failure.
- Potential candidates have to be evaluated early in a specialized center, as the survival rate is worse if the child is transplanted with end-stage liver failure.
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- Immuno-suppression depends on a calcineurin inhibitor (cyclosporin or tacrolimus), and either steroids or an

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induction with a monoclonal antibody against IL2-receptor.
- Early surgical complications are a non-function of the graft (rare), arterial or portal thrombosis, biliary problems (more frequent with partial grafts), bleeding.
- Infections with bacteria and fungi are frequent and often severe. CMV infection is prevented, or screened and pre-emptively treated. EBV infection is frequent and may induce a posttransplant lymphoproliferative disease, that can develop into a lymphoma. Early stages are treated with reduction of immuno-suppression and monoclonal antibodies against CD20.
- Acute rejection is frequent but usually easily controlled. Chronic rejection may be due to poor compliance.
- Late graft loss is due to chronic rejection or long-standing biliary complications.
- Long-term complications are progressive graft fibrosis, renal failure due to drug toxicity (mainly calcineurin inhibitors), and cancers (skin and lymphoma).

Liver transplantation (LTx) in children has developed from the mid-1980s. It has evolved from an emergency life-saving procedure, to the established treatment of liver failure and some liver-based metabolic disorders. It should be performed in specialized centers, where the pre-, per- and posttransplant care is ensured by paediatric hepatologists, surgeons, anesthesiologists, and intensivists, and where all the diagnostic procedures (radiology, endoscopy, immunology, infectiology, pharmacology) can be easily and rapidly performed. The long-term results are very encouraging, but long-term follow-up is mandatory, in order to prevent and treat late complications and graft loss [1].

Indications

The main indications are chronic cholestatic diseases, in first place biliary atresia (60—70% in most centers). Alagille syndrome and progressive familial intrahepatic cholestasis (PFIC) belong also to this group. Metabolic diseases, especially urea cycle disorders, are a rather common indication. For hyperoxaluria type I, the LTx has to be combined with a kidney transplantation. Fulminant hepatic failure, a rare condition in children (viral hepatitis, toxic, metabolic), is the third group of indications. Other cirrhosis (alpha-1-antitrypsin deficiency, cystic fibrosis, autoimmune hepatitis, sclerosing cholangitis) are more seldom an indication, and mostly in adolescents.

The timing of LTx is determined by the liver function, the severity of portal hypertension, the growth failure, other complications such as ascites, infections, hepatopulmonary syndrome, pruritus, the quality of life and the waiting time. In children with biliary atresia and no bile flow, it has to be performed before the age of 3. In metabolic diseases, LTx should be discussed before the development of neurological sequelae due to metabolic decompensations.

Preparation

Potential candidates should be referred to a transplantation centre before the development of end-stage liver failure, in order to decrease the risk of early mortality. Malnutrition is a common complication of chronic cholestasis, and should be corrected before surgery. A careful workup evaluates the cardiac, renal and neurological functions. All vaccinations should be performed, with an accelerated schedule if needed, and especially the live vaccines, as they are contraindicated after transplantation. Psychosocial support should be provided to the families. The cost of the procedure is high (100 to 200,000 Euros, depending on the countries, the length of hospital stay, etc.), and does not include the ancillary costs for families coming from abroad, nor the follow-up visits and drugs. The medical background, and the availability of drugs and monitoring in many countries, may be a limitation before engaging into the process.

Surgery

The organ donor is either a brain dead patient, whose liver will usually be splitted between an adult and a child recipients, or a living donor. The main advantages of living donation are the absence of organ shortage and waiting time, the possibility of planning, the quality of the liver, the short ischemia. The main drawbacks are the risks for the donor, and more frequent biliary complications. There is no clear advantage on the incidence of acute rejection, but maybe on chronic rejection. The decision depends on the child's age (a left lobe fits a young child), local situation (organ shortage, foreigners excluded or not from the waiting list, waiting time, ability to perform adult liver surgery), legal factors (who is allowed to be a donor, a first or second degree relative, a non relative), the technical possibility of safe harvesting of the donor's left lobe or left liver, and the parents' choice. Most grafts in children, whatever the donor, are thus partial livers [2]. The biliary anastomosis is usually done on a Roux-en-Y loop. Full livers of children donors are used for combined Tx, with the kidney (hyperoxaluria type 1), the small bowel (intestinal failure and associated liver disease) or the lungs (cystic fibrosis).

Immuno-suppression

The cornerstome is a calcineurin inhibitor (CNI), cyclosporin or tacrolimus. It is associated with either steroids, or an induction with a monoclonal antibody against the receptor of interleukin 2. Other drugs, such as mycophenolate and mTOR inhibitors, are also used, as renal-sparing agents, or after an episode of rejection.

Short-term complications and management

The early mortality is 10—20%, depending on the indication of transplantation and the general status of the child, and mainly due to surgical complications and infections.

Surgical complications

These are the primary non-function of the liver, rare and necessitating an urgent retransplantation; arterial thrombosis, diagnosed on the daily ultrasonography, re-operated in emergency, with possible evolution toward acute liver failure or biliary necrosis; early bleeding; portal thrombosis,