45b. LONG-TERM COMPLICATIONS AFTER LIVER TRANSPLANTATION
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Due to excellent results in the short-term outcome after liver transplantation, attention has shifted to reducing long-term complications. Seyam et al. investigated late mortality in more than 1000 patients transplanted between 1982 and 1999. Of the 129 who did not survive within this time period, 56% died of side-effects associated with long-term immunosuppression including malignancies and renal impairment, 22% died of vascular complications, and 15% suffered liver organ failure due to recurrent disease [1].

45b.1. Opportunistic Infections

Opportunistic infections are primarily viral and fungal in origin. Cytomegalovirus (CMV) is a frequent cause of infection in the post-transplant setting. Diagnostic assays, such as CMV pp65 Ag and quantitative PCR have demonstrated similar efficacy for the diagnosis and monitoring of CMV infection in liver transplant recipients [2]. Persistent CMV infection has been shown in patients with chronic rejection [3]. Valganciclovir is an oral prodrug for ganciclovir [4] and has various advantages over the original formulation (10 times higher bioavailability, lower application frequency, lower occurrence of resistance). A high viral load of Epstein-Barr infection and a high level of immunosuppression are reported as risk factors for post-transplant lymphoproliferative disease (PTLD) [5]. The clinical presentation varies and may manifest as an impaired general condition with fatigue, weight loss, tonsillitis, lymph node enlargement, and gastrointestinal symptoms. PTLD is more frequent in children after organ transplantation, but still represents 15% of tumors in adults. The treatment includes modulating the immunosuppressive regimen and applying antiviral drugs such as acyclovir or ganciclovir, and as a second step, treatment with anti-CD20 monoclonal antibodies if CD20 positive tumor cells are detectable.

The clinical manifestation of infection with human herpes virus-6 may vary between asymptomatic infection to severe symptoms [6]. Other viral pathogens include herpes simplex virus and varicella. Fungal infections in transplanted patients include infection with Candida sp., Aspergillus, Cryptococcus, and Histoplasma. Early diagnosis and careful management of disseminated fungal infections are necessary to avoid high morbidity and mortality rates.

45b.2. Chronic Rejection

Advances in immunosuppressive regimens have greatly reduced the incidence of rejection and allograft failure. Chronic rejection begins within weeks to months or years after OLT and affects about 4% to 8% of patients [7]. Risk factors for chronic rejection include alloimmune immunologic injury and nonimmunologic factors such as older donor age, prolonged cold ischemia, and donor atherosclerosis. The most widely recognized manifestation of chronic rejection is obliterator arteriopathy [8]. Chronic rejection may appear in dolently and might only become apparent as liver test injury abnormalities (yGT, AP, bilirubin, transaminases). The diagnosis needs to be confirmed by histopathologic examination. It is important to recognize chronic rejection in the early stages in order to avoid irreversible damage to the allograft. The first therapeutic approach is generally treatment with corticosteroids. At our transplant center and in some others, this step is often accompanied by switching the baseline immunosuppression from CSA to TAC and initiating mycophenolate mofetil (MMF) rescue therapy [9]. A recent study investigating the efficacy and safety of anti-interleukin (IL -2) receptor antibodies (daclizumab and basiliximab) for steroid-resistant rejection revealed a poor histologic response to chronic rejection but successful resolution (75%) in patients with acute cellular rejection [10].

45b.3. CNI-Induced Nephrotoxicity

Despite the introduction of new immunosuppressive agents (table 45b.1), CNI remain the key drugs of most immunosuppressive regimens. Both CSA and TAC inhibit the calcineurin-calmodulin complex and therefore IL-2 production. Complications of CNI, including
nephrotoxicity, diabetes, hypertension, and hyperlipidemia, have a major effect on morbidity and mortality within the transplant setting. CSA monitoring has traditionally been performed by measuring predose “trough” blood concentrations (C0). The development of a 2 hour post-dose CSA (C2) monitoring strategy has emerged as a more sensitive approach for assessing pharmacokinetics and provides greater precision in the optimization of dosing than C0 measurements. The incidence of chronic, CSA-induced, mild to moderate nephrotoxicity (serum creatinine > 125 and < 200 umol/L) is high and varies in different studies between 23.3% and 78.0%. The incidence of severe chronic renal failure ranges from 4-28%, and the incidence of end-stage renal insufficiency resulting in hemodialysis is 1.4-7.9% [11].

In OLT patients with CNI-induced nephrotoxicity, a complete replacement of CNI with conversion to MMF bears an increased risk of acute rejection ranging from 0% to 60% [12-15]. MMF inhibits inosine monophosphate dehydrogenase, a critical enzyme in the de novo pathway of purine synthesis. It may be used for acute or chronic rejection, recurrent autoimmune disease, and corticosteroid resistance.

Results from previous studies with immunosuppressive regimens including MMF and reduced CNI treatment suggest a significant improvement in renal function in this patient group [16-18]. In contrast, Neau-Cransac et al. [19] and Gonwa et al. [20] did not find a significant renal function improvement after withdrawal of CNI and introduction of MMF. We investigated the impact of combined MMF and minimized CNI therapy on cardiovascular risk factors, liver parameters, and renal function [21]. We randomized 32 patients with CNI-induced renal dysfunction to either a) continue their current CNI dose or b) to receive MMF up to a dose of 1000 mg twice per day followed by stepwise reduction of CNI (TAC trough levels < 4 ng/ml, CSA trough levels < 50 ng/ml). Three months after conversion therapy, we observed a significant decrease in the mean values of serum creatinine (from 1.88 ± 0.36 to 1.58 ± 0.33 mg/dL; p < 0.001), serum urea (from 39.2 ± 11.8 to 29.9 ± 9.59 mg/dL; p < 0.001), and GFR (from 51.4 ± 10.8 to 61.6 ± 14.1 mL/min; p < 0.001, fig. 45b.1). Interestingly, renal function improved even in long-term liver transplant recipients (5.6 ± 3.6 years; range 2-13 years), which suggests at least a partial reversibility of CNI-induced renal damage.

![Figure 45b.1](image-url)