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ORIGINAL ARTICLE

Liver transplantation in patients with liver cirrhosis and active pneumonia: an observational study

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Summary

Patients with chronic liver disease are at high risk for severe infection because of increased bacterial translocation and immune suppression associated with liver dysfunction. Patients presenting with severe pneumonia and acute decompensation of cirrhosis are generally not considered for liver transplantation because it is unknown if these patients can recover from infection while under immunosuppression. We performed an observational study where patients with cirrhosis of the liver remained on the waiting list, although suffering from active pneumonia. Nine patients were included, but only six patients improved under goal-directed therapy and subsequently underwent liver transplantation. All six patients recovered quickly from infection; five patients recovered without sequelae and one patient died because of late complications. We propose that in patients with chronic liver disease and active pneumonia transplantation is a treatment option that should not hastily be abandoned.

Introduction

Bacterial infection, especially with intestinal-type bacterial flora, is a common complication in patients with cirrhosis [1]. Almost 50% of hospitalized patients with cirrhosis develop bacterial infection [2]. Spontaneous bacterial peritonitis, urinary tract infection, and pneumonia are the most frequent infective complications in this group [2]. Infections are mostly community acquired but also nosocomial and may also be combined [2]. Experimental studies and the spectrum of causative organisms suggest that increased bacterial translocation is the main cause for infections [1]. But patients with cirrhosis also suffer from severe dysfunction of the immune system [3], as the liver function is essential for local and general immune response [4–6]. It follows that mortality rates in cirrhotic patients suffering from severe infection are as high as 40% [1].

Typically such patients would not have been considered for liver transplantation because of their need for immunosuppression after orthotopic liver transplantation (OLT). But the allocation systems in many countries have been changed to mainly consider the necessity for an organ and not prognosis after transplantation as the pivotal criteria. And it has been shown that, indeed, after introduction of the Mayo end-stage liver disease (MELD) allocation system mortality in waiting list has decreased substantially [7]. However, this leads to a shift of the mortality in waiting list to post-transplant phase [8]. Practically, in Germany mortality after liver transplantation increased significantly after implementation of the MELD allocation system and now the 1-year survival rate

may reach as low as 60% depending on the transplant center. This is attributed to the fact that only critical ill patients (MELD greater 30 and above) get an offer and are being transplanted [8]. As a consequence, we have many patients with compensated cirrhosis that do not receive an organ because of their low MELD score. Then these patients suffer from infection and may subsequently also develop acute-on-chronic liver failure (ACLF). Now they would readily receive an organ because of their high MELD score, but because of active infection would be excluded from transplantation.

In this situation, we defined certain conditions under which we would perform liver transplantation in patients while suffering from severe pneumonia. Furthermore, we defined an algorithm for peri-operative goal-directed treatment. Herein, we report the results of six patients who were included in this observational study and underwent liver transplantation.

Methods

Based on clinical experience after introduction of the MELD allocation system, we decided in a multi-disciplinary panel to define criteria upon which patients on the waiting list suffering from active pneumonia may undergo transplantation. Included patients had to fulfill common criteria for pneumonia causing severe sepsis (defined as sepsis with organ dysfunction other than liver) or septic shock [9]. Pneumonia was defined according to common guidelines [10,11], i.e., a radiographic infiltrate that is new or progressive, along with clinical findings suggesting infection, which include the new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation. According to our clinical routine, we also confirmed diagnosis by bronchoalveolar lavage where possible but in some cases we only obtained tracheal swap cultures and did not enforce further invasive measurements if not necessary.

We also defined further criteria which patients had to fulfill to be included and which we considered necessary for an acceptable prognosis after OLT:

1 Prior to decompensation patients had to be in stable, compensated state (Child A) for 6 or more months.
2 Patients had to have stable heart function with ejection fraction >50%.
3 Patients should have no chronic lung disease.
4 Age should be 65 years or younger.
5 Prior to decompensation patients should have only mild kidney dysfunction (estimated glomerular filtration rate >50%) and acute kidney injury should be considered reversible.

After inclusion, we immediately initiated goal-directed therapy and, if not already conducted, the following measures were executed according to appropriate guidelines (see references):

1 Placement of a central venous line for continuous measurement of central venous oxygen saturation and central venous pressure [12].
2 Assessment of airway intubation and, if necessary, lung-protective ventilation with lower tidal volumes [13,14].
3 Administration of crystalloids and albumin to maintain a central venous pressure of 8–12 mmHg and serum albumin of at least 4 g/dl [14,15].
4 Norepinephrine was used to maintain a mean arterial pressure above 65 mmHg; when cardiac output remained low despite adequate fluid resuscitation dobutamine was used.
5 After obtaining cultures, we administered empirical broad spectrum intravenous antibiotics (imipinem/cilastatin and linezolid) in combination with antifungal therapy (fluconazole) [12].
6 Early initiation of renal replacement therapy such as continuous veno-venous hemofiltration [16].
7 Selective digestive tract decontamination to reduce bacterial translocation [15] and hepatic encephalopathy [17] (and improve overall survival [18]).
8 We also recommended early transfusion of erythrocyte concentrates and fresh frozen plasma, although we did not define a certain threshold for transfusion [12,14].

In contrast to published recommendations or guidelines [12,14], we did not plan to administer activated protein C or corticosteroids because we considered it detrimental for liver transplantation. We then planed to assess the clinical course of the patient over 48 h and only proceed with transplantation when the patient did not deteriorate. Deterioration was defined as any of the following:

1 Increasing need for vasopressor support.
2 Severe increase of laboratory markers for infection.
3 Aggravation of radiological sings for pulmonary infiltrates.
4 Decreasing ratio of PaO_2 (partial pressure of oxygen in arterial blood) and FiO_2 (fraction of inspired oxygen).

After inclusion of a patient, we transferred all clinical variables and regular laboratory measurements to a study specific database. Regular laboratory measurements included white blood count (WBC), liver function tests, and creatinine. Procalcitonin (PCT) was also included but not C reactive protein because PCT allowed for better guidance of antibiotic therapy [19] and is also a valid marker of infection in patients with cirrhosis of the liver [20] or after liver transplantation [21]. Liver function tests included total serum bilirubin, alkaline phosphatase, gamma-glutamyl transferase, aspartate and alanine transaminase, and international normalized ratio of

prothrombin time (INR). Patients also received chest X-ray at regular intervals. According to clinical routine, we determined the simplified acute physiology score (SAPS) II (which has also been validated in patients suffering from liver cirrhosis) [22] on admission to the intensive care unit and at regular intervals to asses disease severity and associated mortality.

Results

In the period between January 2010 and March 2011, we had 163 patients on the waiting list of which 68 underwent regular transplantation; 83 patients remained on the waiting list or dropped out from the waiting list; and 12 patients were screened for inclusion in the study (see Fig. 1). Three patients did not fulfill the inclusion criteria because of pre-existing severe renal dysfunction (two patients) or low ejection fraction in echocardiography. Nine patients were included in the study and underwent goal-directed therapy as described above. Three patients deteriorated according to the above criteria, did therefore not undergo transplantation and subsequently died because of multiorgan failure.

Six patients finally remained on the waiting list while suffering from active pneumonia and were included in this report (see Table 1 for summary of patient characteristics). Three patients suffered from in-hospital (HAP, patient 2) or ventilator-associated pneumonia (VAP, patients 1 and 3) following complicated colorectal surgery (patient 1) or variceal bleeding (patient 2 and 3). Patient 4 through 6 presented with community-acquired pneumonia (CAP). In all cases, pneumonia was diagnosed by unequivocal radiological evidence of typical infiltrates in chest X-ray or computed tomography. In all patients, we obtained cultures from bronchoalveolar lavage or tracheal swap. In all but one patient we could identify potentially pathological agents (see Table 1).

Before the development of pneumonia, the patients had only mild symptoms of chronic liver failure, corresponding to Child-Pugh-Turcotte class A with median MELD of 12 (range 8–14). All patients subsequently developed severe liver dysfunction that fulfilled criteria for ACLF [23]. Because of further aggravation of infection and ACLF under standard therapy patients were ultimately transferred to the intensive care unit. On admission to the intensive care unit, they had SAPS II of 45 to 63 corresponding to a predicted mortality of 35% to 74%. Furthermore, all patients suffered from acute kidney injury and patients 1 and 2 received continuous veno-venous hemofiltration before transplantation.

All six patients had modest improvement under goal-directed therapy, i.e., decreasing the need for vasopressor

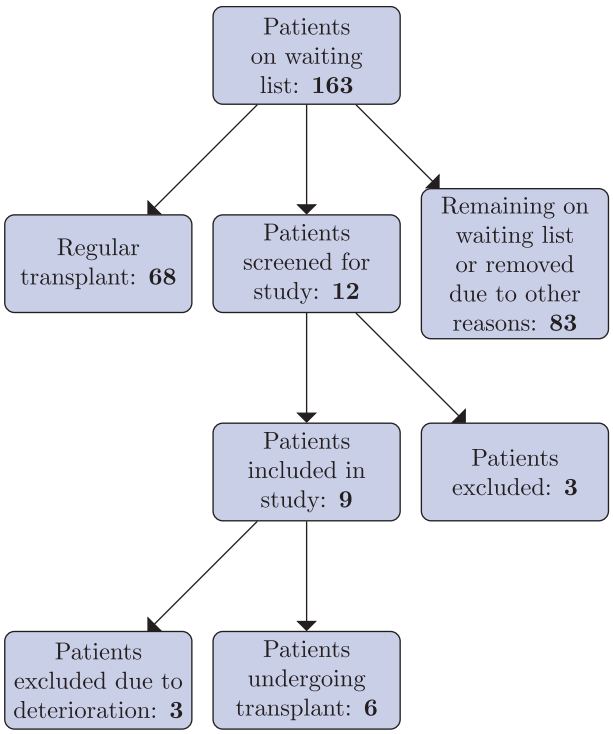

Figure 1 Flow chart of patient selection.

Table 1. Summary of patient characteristics. Potentially causative agents were obtained from bronchoalveolar lavage or tracheal swap culture.

No	Gender	Age (years)	Liver disease	Cause of decompensation	Type of infection	Potentially causative agent	SAPS	MELD
1	M	57	HBV cirrhosis	Postoperative	VAP	*Pseudomonas aeruginosa*, *Candida* sp.	63	40
2	M	54	Alcoholic cirrhosis	Variceal bleeding	HAP	*Candida* sp.	59	40
3	M	60	Alcoholic cirrhosis	Variceal bleeding	VAP	*Candida* sp., *Enterococcus* sp.	60	35
4	F	57	Alcoholic cirrhosis	Infection	CAP	*Bacteroides*, *Candida albicans*, *Clostridium* sp.	55	32
5	M	62	HCV cirrhosis	Infection	CAP	Unknown	45	27
6	M	45	Alcoholic cirrhosis	Infection	CAP	*Klebsiella pneumonia*, *Pseudomonas aeruginosa*	47	28

HBV, hepatitis B virus; HCV, hepatitis C virus; VAP, ventilator-associated pneumonia; HAP, hospital-acquired pneumonia; CAP, community-acquired pneumonia; SAPS, simplified acute physiology score II at admission to the intensive care unit; MELD, model for end-stage-liver disease.

support and/or decreasing leukocyte count. The extent of pulmonary infiltrates did not change significantly as well as parameters of oxygenation. All six patients received an acceptable organ offer within 24–48 h after termination of the observation period (within the observational period we declined all offers) and underwent liver transplantation. The quality of donors and transplanted organs was not significantly different compared with regular transplantation with a median donor risk index [24] of 1.514 (range 0.973–2.050).

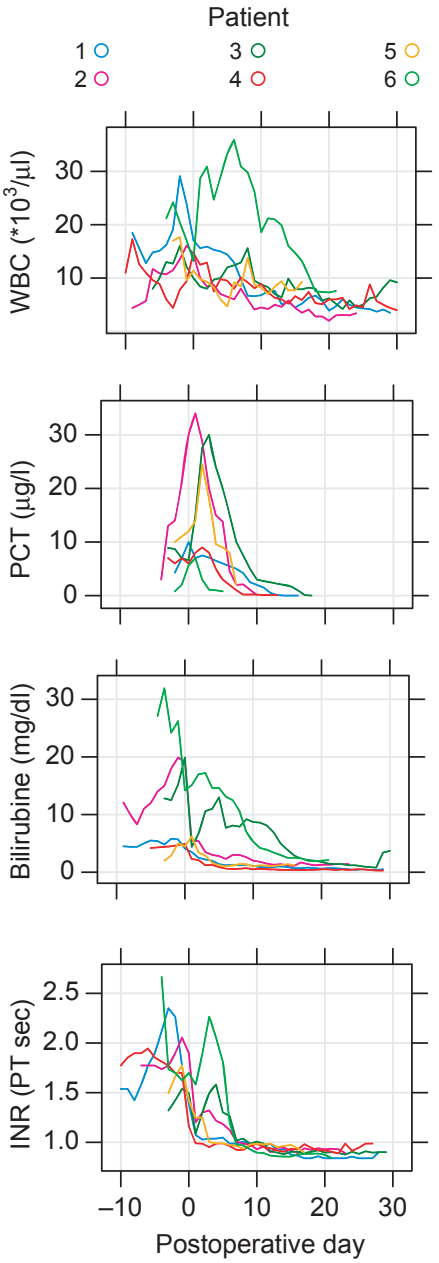

Figure 2 Laboratory values of patients. WBC, white blood cell count; PCT, procalcitonin; INR (PTsec), international normalized ratio of prothrombin time.

There were no intraoperative complications and after liver transplantation, we initially continued the goal-directed therapy. Patients also received basiliximab and corticosteroids for induction of immunosuppression and immunosuppression was continued with mycophenolate mofetil and corticosteroids from postoperative day (POD) 1. According to standard practice in patients with renal dysfunction, tacrolimus and/or everolimus were/was delayed until POD 5 or later. Thereafter dose was adjusted to reach trough levels of 5–10 µg/l or 4–8 µg/l for tacrolimus and everolimus respectively. Antibiotic therapy was continued for at least 10 days and then guided by radiological and clinical examination and laboratory tests (mainly WBC and PCT).

Clinical signs of infection (fever, purulent sputum, and multiorgan dysfunction) rapidly decreased in all six patients and neither of them required any vasopressor support after POD 3. WBC and PCT also decreased rapidly after transplantation in all five patients (see Fig. 2). Furthermore, radiological examination of the chest showed resolving lung infiltrates (see Fig. 3) and extubation could be achieved by POD 5. All six patients were clinically free of infection by POD 10. Liver function was adequate in all three patients with INR and transaminases within normal range by day 12 and no signs of cholestasis. Two patients required hemofiltration and/or hemodialysis after transplantation for more than 1 week; all other patients showed signs for acute kidney injury but did not require renal replacement therapy.

In all patients except patient 3, the further course was uneventful and they could be discharged within 30 days after OLT. Patient 3 suffered from multiple postoperative complications including acute kidney injury requiring renal replacement therapy, recurrent bleeding requiring surgery, and critical illness polyneuropathy with complicated weaning from the respirator. Although the patient had slow but constant progress, was free from pulmonary infection, and could be transferred to intermediate care ward between times, he finally suffered from cytomegalovirus colitis, had to be re-intubated, and died from septic shock 3 months after OLT. All other patients are alive and in good health with a median follow-up of 8 months (range 4–16 months).

Discussion

Here we present six patients who underwent OLT, although they suffered from active pneumonia at the time of transplantation. Patients were selected on the basis of predefined criteria and underwent transplantation if they did not show deterioration within 48 h after initiation of

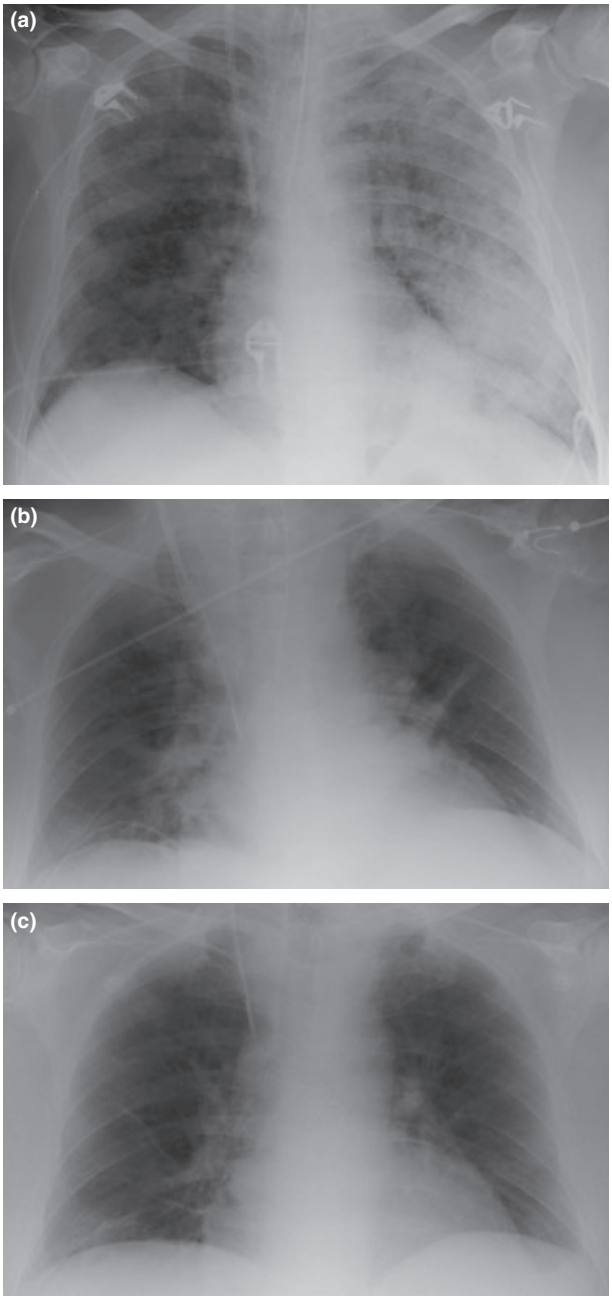

Figure 3 Chest X-ray of patient 2, 2 days before orthotopic liver transplantation (OLT, a), at 1 week (b) and 2 weeks (c) after OLT. Before OLT, the patient had pulmonary infiltrates predominantly on the left side and bilateral pleural effusion. One week later pleural effusion and infiltrates have almost disappeared. Two weeks after transplantation, the patient had chest X-ray without further pathological findings.

goal-directed therapy. Overall six patients were excluded either because they did not fulfill the inclusion criteria or they did not show any response to multimodal anti-infective treatment. Of the six patients included, all showed clear radiological signs of pneumonia along with other signs of infection and therefore fulfilled common diagnostic criteria for pneumonia [10,11].

Bronchoalveolar lavage or tracheal swap cultures showed a high incidence of *Candida* species. This may be attributed to selection criteria as all included patients did not improve under conventional treatment of pneumonia, but mere colonization may also not be ruled out. Furthermore, we could not identify any causative agent in at least one patient (and possibly more patients with candida colonization), which is a known problem especially in patients with CAP [10]. Our initial goal-directed therapy includes a very broad anti-infective regimen even in cases of CAP, because patients deteriorated under conventional antibiotic therapy and we expected a high prevalence of fungi and highly resistant bacteria [14]. After transplantation and identification of possibly causative agents, we de-escalated the anti-infective regimen.

All patients primarily suffered from infection but developed severe liver dysfunction later on that fulfilled criteria for ACLF [23]. Infection has been recognized as one of the main causes for ACLF, but many patients who primarily present with ACLF because of other causes also develop infection [23]. Chan *et al.* reported on a cohort of patients in the latter situation and could show acceptable outcome after liver transplantation [25].

In our cohort of patients, we also observed rapid recovery from infection within 2 weeks after transplantation. Our clinical experience suggests that this is not merely attributed to goal-directed therapy but also may be attributed to the restoration of liver function in these patients. Differentiation of these effects is only possible in a randomized, controlled trial; but such a trial would surely face ethical objections. At least compared with a nontransplant cohort of patients, Pellegrino *et al.* could show comparable outcome of VAP in patients after OLT [26]. So far there have been no reports concerning patients suffering from active pneumonia before major abdominal surgery and their postoperative outcome, although in rare cases emergency surgery has to be performed also in patients suffering from pneumonia. There have been some reports on thoracic surgery in patients with pneumonia and these indicate that the rate of complication is higher in these patients [27].

Only one patient succumbed to multiple postoperative complications that were not related to his initial infection but may rather be attributed to long-term multi-organ dysfunction often observed in these high MELD patients. In the six included patients, this corresponds to a survival rate of 83% (with a median follow-up of 8 months) and is comparable with the survival rate in our general cohort of transplant recipients of 80% after 12 months.

In conclusion, we could show that infection in patients with cirrhosis that subsequently leads to aggravation of the liver function is not necessarily a contraindication for liver transplantation. If patients are carefully selected and undergo goal-directed anti-infective therapy, transplantation may be an effective measurement to reconstitute not only the liver function but also an effective host defense. We therefore propose to apply our concept of goal-directed therapy in a larger cohort of patients to improve patient selection and outcome in patients with liver cirrhosis and active infection.

Authorship

AG, TT, TL, GR and AO: designed the study. AG, WA, AO and TL: performed the study. AG and WA: collected and analyzed the data. AG, AO and TT: wrote the paper. GR, TL and MB: critically reviewed the paper.

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