

Budd-Chiari syndrome management: Lights and shadows

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Abstract

Budd-Chiari syndrome (BCS) is a rare disease whose management should follow a step by step strategy. Anticoagulation and medical therapy should be the first line treatment. Revascularization or TIPS are indicated in case of no response to medical therapy. OLT should be indicated as a rescue therapy and anticoagulation be started soon after OLT. However, no clear indication can actually be given about the timing of different treatments. Moreover, there is some concern about treatment of some subgroup of patients, especially regarding the risk of recurrence after liver transplantation. The topic of this paper is to critically review the actual knowledge of BCS management.

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Key words: Budd-Chiari syndrome; Management; Liver transplantation

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TIMING OF TREATMENT

It is widely accepted that the management of Budd-Chiari syndrome (BCS) should follow a step by step strategy. In fact, recently published guidelines suggest medical therapy (anticoagulation, treatment of underlying disease, symptomatic therapy of portal hypertension complications) as the first-line treatment, angioplasty/stenting the second-line (in patients with short-length stenoses not responding to medical therapy), TIPS the next step (in patients not responding to medical therapy and in case of no response to, or stenoses unsuitable for, angioplasty/stenting) and liver transplantation (LT) as the last chance when TIPS is not effective. However, as emphasized by the authors, the definition for response to therapy was not stated^[1].

A recent proposal of the definition for response to BCS treatment has been published, as described in Table 1. The response was defined as *Complete* when there was no ascites, Na and creatinine were normal with no or low-dose diuretics (spironolactone 75 mg or furosemide 40 mg/die), there was a Factor V increase > 40% of the normal range, a bilirubin decrease < 15 mmol/L, no portal hypertension bleeding or spontaneous bacterial peritonitis and BMI was > 20 Kg/m². The response was defined as *Ongoing* when ascites was detectable but responsive to low-dose diuretics, Na and creatinine were normal, Factor V was increasing (if initially low) and bilirubin decreasing (if initially high). *Treatment Failure* was defined when criteria for complete or ongoing response were lacking. Following this strategy, 51 consecutive BCS patients were treated, obtaining a 5-year survival of 89%^[2]. However, this proposal of a definition remains the only one actually published, reflects the experience of a single group and surely needs validation^[1]. Moreover, it has to be stated if considering a treatment failure when the progression of liver disease is evident but outside the above definition, like in the case of histological progression (severe fibrosis/cirrhosis) or of worsening portal hypertension (new appearance or increasing size of esophago-gastric varices). Furthermore, to better understand

Table 1 Definition for response to Budd-Chiari syndrome treatment^[2]

Complete response	No ascites Normal Na and creatinine with no or low-dose diuretics (spironolactone 75 mg or furosemide 40 mg/die) Factor V increase > 40% of the normal range Bilirubin decrease < 15 µmol/L No portal hypertension bleeding No spontaneous bacterial peritonitis Body mass index > 20 kg/m ²
Ongoing response	Ascites detectable but responsive to low-dose diuretics Normal Na and creatinine Factor V increase (if initially low) Bilirubin decrease
Treatment failure	When criteria for complete or ongoing response were lacking

the correct timing of therapy in BCS management, the efficacy of each treatment should be observed in a larger number of patients and be durable during follow up.

The outcome of BCS with currently available treatment is described in a recently published prospective multi-center study in which 163 BCS patients were followed for a median of 17 mo (range 1-31 mo); 18% had also portal vein thrombosis, 84% had a thrombophilic syndrome, 46% of which a myeloproliferative disorder (MPD). Overall, 29 died [8 liver failure, 2 multiple organ failure (MOF), 2 bleeding]. The 24 mo survival was 82% (24 mo LT Free Survival 68%). Prognostic factors were sex (male), ascites and creatinine. Importantly, about 1/3 of the patients remained on medical therapy only^[3]. However, the follow-up was not long enough to eventually show the consequences of a slowly progressing disease, possibly prevented by early recanalization/decompression, and to draw any definitive conclusion about the exact timing of treatment. Furthermore, we wonder if early decompression could stop or reverse histological progression of hepatic disease, finally improving long-term outcome.

RECANALIZATION OR DECOMPRESSION OF BUDD-CHIARI SYNDROME

In the case of short-length stenoses, angioplasty/stenting is a therapeutical approach suitable for BCS with a good medium term outcome in some experience^[4-6]. However, no data can argue against the use of TIPS also in the subgroup of patients with short-length stenoses since a prospective comparison between TIPS and angioplasty/stenting has not been performed, to our knowledge. Such a therapeutical choice in this subgroup of patients should be based on local expertise.

TIPS is surely the mostly used treatment for BCS when medical therapy fails^[2,3]. In early experiences, TIPS has proved effective as BCS treatment^[7-9]. Moreover, TIPS can be successful also in the technically difficult case of extension of thrombosis to the portal vein tree^[10,11]. Recently, a multi-center study provided long-term data on TIPS treatment for 147 BCS patients not responding to medical treatment or recanalization. TIPS was success-

ful in 124 BCS patients, who were followed for a median of 36.7 mo. Overall, 16 (13%) died, 8 (6.5%) underwent OLT. Main complications were hepatic encephalopathy in 21% and TIPS dysfunction in 41% (significantly less in PTFE-covered than in Bare stents). The 10-year survival was 69%. Prognostic factors were age, bilirubin and INR^[12].

LIVER TRANSPLANTATION FOR BUDD-CHIARI SYNDROME

LT is the last chance for BCS syndrome non responsive to either medical therapy or recanalization/decompression^[1,13-16]. A European multi-center study reported long-term data on 248 patients who underwent LT for BCS between 1988 and 1999. MPD was the underlying syndrome in 45%. LT was performed electively in 55%, in emergency in 21%. Hepatic cellular cancer was incidentally found in explanted liver in 3. Before LT, 19% had portal vein thrombosis and 16% Inferior vena cava thrombosis. Median follow-up was 48 mo. Overall, 67 (27%) died (49% in the first month). Causes of death were sepsis in 47%, graft dysfunction or hepatic artery thrombosis in 19%, venous thrombosis in 12%, cardiac in 9% and brain damage in 5%. There was a significantly increased mortality if LT was shortly after SPSS or TIPS. Thirty-seven patients underwent re-LT (4 twice). The 10-year survival was 68%. After 1 year there were 9 deaths, seven of which were in MPD patients. Causes were: 4 BCS recurrence, 1 leukaemia (7 years post-LT), 1 ovarian cancer, 1 colangitis, 2 not known. Anticoagulation after LT was performed by 200/235 (18 heparin or aspirin), suspended in 10, all of which were believed to have a cause of BCS reversible after LT (antithrombin III and Protein C deficiency); all had an uneventful outcome but one who reported pulmonary embolization 1 year after, when anti-phospholipid syndrome was discovered. Complications post-OLT in the patients treated with anticoagulation were thrombosis in 27 (11%), 11 of whom (41%) died; recurrence of BCS in 6 (1 Re-OLT, 1 TIPS, 4 death); bleeding in 27 (11%), 2 of whom died (intracranial bleeding). Prognostic Factors were pre-OLT renal function and pre-OLT SPSS/TIPS^[17]. However, the

prognostic factor of a previous shunt before LT has to be weighed cautiously because it can only reflect the fact that patients who underwent TIPS before LT had the most severe liver disease. Moreover, a recent American multi-center study found no negative effect of TIPS on the following LT outcome^[18]. Finally, recent data show promising results of living donor LT for BCS^[19].

The possibility of BCS underlying disease progression is a concern, in particular the development of leukaemia in MPD after LT. Preliminary multi-center studies failed to draw conclusions on this topic, given that long-term outcome was not correlated to the type of underlying disease predisposing to BCS^[10,11]. However, although not statistically significant, 7 of the 9 patients who died after 1 year post LT in the European study had MPD^[10]. The impact of Jak2 and MPL mutations on prognosis of splanchnic vein thrombosis (either BCS or portal vein thrombosis) was recently reported in 241 cases. In BCS, patients with the Jak2V617F mutation had a significantly more severe disease (Child-Pugh, Clichy PI, Rotterdam score). Moreover, event free survival tended to be decreased, but not significantly, in patients with Jak2V617F mutation and significantly decreased in MPD. However, at a median follow up of 3.9 years, overall survival was not influenced by either Jak2V617F mutation or MPD^[20].

CONCLUSION

BCS should be treated following a step by step strategy. Anticoagulation and medical therapy should be the first line treatment. Revascularization or TIPS are indicated in case of no response to medical therapy. OLT should be indicated as a rescue therapy and anticoagulation be started soon after OLT. However, given that accepted criteria of response to therapy is still lacking, the timing of treatment, in particular TIPS, should be re-evaluated in future, well-designed multi-center studies.

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