Budd–Chiari Syndrome and Myeloproliferative Neoplasms

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Abstract

Non-cirrhotic and non-malignant splanchnic vein thrombosis (SVT) recognizes Philadelphia-negative myeloproliferative neoplasms (MPN) as the most frequent systemic cause. An overt MPN is diagnosed in 40% of the patients with Budd–Chiari syndrome (BCS). In BCS patients, the MPN molecular hallmark JAK2 V617F is present in up to 80% of those with overt MPN and up to 43% of those without an overt diagnosis according to the WHO criteria. In those latter, the other MPN driver mutations in the JAK2 exon 12, CALR, and MPL genes are infrequent.

Treatment of the acute phase of BCS does not differ from that employed in non-MPN patients and is based on immediate anticoagulation with heparin, together with endovascular treatment with a transjugular intrahepatic portosystemic shunt and/or angioplasty/stenting. In the case of no response to such treatments, liver transplantation is the only reliable option for treatment of BCS, and the presence of MPN does not influence the survival outcome. Indefinite treatment with oral anticoagulation based on vitamin K-antagonists is recommended in all BCS patients. Cytoreduction is warranted in all MPN patients with thrombosis, but its efficacy in preventing recurrent thromboses is doubtful in the patients with SVT.

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6.1 Introduction

The estimates of the incidence of Budd–Chiari syndrome (BCS) differ widely depending on the studies, which are mainly based on national or regional computerized hospital registries [1, 2]. The incidence per million inhabitants (pmi) of newly diagnosed BCS has been reported between 0.13 and 0.50 before 1990, and between 0.3 and 0.8 afterward [1, 2]. Two recent population-based studies conducted in Italy and France and based on the hospital discharge codes estimated an incidence rate of 2.1 pmi [3] and 4.1 pmi [4], respectively; in the French study, the incidence rate of non-cirrhotic and non-malignant BCS resulted in 2.1 pmi [4]. In the last two decades, non-invasive imaging methods, such as Doppler ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), have been substantially improved and broadly employed, giving a reason of the much higher incidence reported in recent studies [1, 2]. The risk factors for BCS can be local or systemic, and inherited or acquired conditions influence the latter. Malignancy, cirrhosis, infectious or inflammatory diseases, abdominal surgery or trauma, thrombophilia, and myeloproliferative neoplasms (MPN) are common conditions associated with BCS; sex-associated risk factors are the use of oral contraceptives, hormone replacement therapy, pregnancy, and puerperium [5]. Multiple concurrent factors are combined in up to half of the patients with BCS [5].

6.2 Budd–Chiari Syndrome and Myeloproliferative Neoplasms

The updated WHO classification of Philadelphia-negative MPNs includes polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), the latter including prefibrotic/early primary myelofibrosis (prePMF) [6]. These disorders are characterized by stem cell-derived clonal myeloproliferation with mutually exclusive JAK2, CALR, and MPL mutations [7]. Thrombotic complications or transformation into secondary myelofibrosis or leukemia can complicate the natural history of MPN [8]. Thromboses involve venous vessels in about one-third of cases. In contemporary cohorts of MPN patients the incidence of overall thrombosis/venous thromboembolism (VTE) per 100 patient-years was 2.6/1.0 in PV [9, 10], 1.9–2.1/0.6 in ET [11, 12] and prePMF [11, 13], and 1.75/1.0 in PMF [14]. The incidence of VTE per 100 patient-years is definitely higher than the 0.1–0.2 rate of major VTE recorded in the general population of Western countries [15].

In a recent population-based study, the rate of early VTE after diagnosis was nearly 10-fold increase in the MPN patients in comparison with the control participants, declining with the follow-up to a 3.2-fold increased rate [16]. In addition, the rate of splanchnic vein thrombosis (SVT) was substantially higher around the time of MPN diagnosis, with hazard ratio (HR) values of 81.1 (95% CI 22.0–300), 12.5 (95% CI 6.4–24.5), and 4.3 (95% CI 2.7–6.8) at 3 months, 1 year, and 5 years after MPN diagnosis, respectively, compared with control participants [16]. The ratio between the rate of thrombotic events recorded in the MPN patients and that of the general population is maximal considering BCS; in fact, during the follow-up after diagnosis BCS occurs in 0.3–2.9% of the patients [17], which is greatly over-represented in comparison with the prevalence of 1.4–4.0 pmi reported in the Western populations [4, 18]. In a pooled cohort of 1500 patients with MPN and thrombosis, BCS accounted for 2.5% of overall cases and 6.9% of the cases with VTE [19].

In two population-based studies, MPN emerged as the condition more frequently associated with BCS, accounting for 38–48% of cases [4, 18]. A meta-analysis carried out on 555 patients with BCS demonstrated that the prevalence of overt MPN diagnosed after a complete diagnostic work-up was 31.8% in the patients without cirrhosis and hepatobiliary cancers [20]. Another meta-analysis conducted according to the same criteria in 1062 patients with BCS reported a prevalence of overt MPN as high as 40.9% [21] (Table 6.1). In the same meta-analyses, the rate of MPN in patients with extra-hepatic portal vein obstruction (EHPVO) was 16.1% and 31.5%, respectively [20, 21] (Table 6.1). PV is the most common type of MPN in patients with BCS (52.9%), followed by ET (24.6%) and PMF (6.7%) [21].

By comparison, in a meta-analysis conducted in BCS patients, the pooled prevalence of deficiency of natural anticoagulants antithrombin, protein C, and protein S was 9.1% [22]. A prevalence of 2.3% (superimposable to that of the

Table 6.1 Prevalence of myeloproliferative neoplasms (MPN) and the JAK2 V617F mutation in patients with splanchnic vein thrombosis (SVT): Budd-Chiari syndrome. (BCS) and extra-hepatic portal vein obstruction (EHPVO). Modified from De Stefano et al. [30]

Reference	Type of SVT	*n* patients	JAK2 V617F, (*n*, %)	Overt MPN (*n*, %[a])	JAK2 V617F (*n*, %[a])		
					All patients[a]	MPN patients[a]	Non-MPN patients[a]
Qi et al., 2011 [20], Meta-analysis	BCS	555	177/555 31.8%	77/242 31.8%	106/242 43.8%	62/77 80.5%	44/165 26.6%
	EHPVO	858	250/858 29.1%	86/532 16.1%	136/532 25.5%	75/86 87.2%	61/446 13.6%
Smalberg et al.,2012 [21] Meta-analysis	BCS	1062	159/401 41.1%	180/440 40.9%	188/440 42.7%	144/180 80.3%	44/260 17.1%
	EHPVO	855	166/595 27.7%	188/615 31.5%	228/615 37.0%	162/188 86.6%	66/427 15.4%

[a]Including only patients with non-cirrhotic and non-malignant SVT who received a complete diagnostic work-up for MPN

general population) of the prothrombin G20210A mutation has been reported in patients with BCS, whereas factor V Leiden mutation is much more frequent, up to 24.9% [23].

6.3 Molecular Diagnosis of MPN-Related Budd–Chiari Syndrome

Given the high rate of MPN as an underlying cause of BCS and SVT, the current practice guidelines recommend the routine screening for MPN [24–27]. However, the diagnosis of MPN in this setting is somewhat difficult, because splenomegaly is mistakenly associated with the occurrence of portal hypertension, hypercythemia is often masked by portal hypertension-related hypersplenism and hemodilution or gastrointestinal bleeding, and hepatic ischemia in BCS patients can produce an inappropriately elevated level of erythropoietin [28, 29]. Therefore, a deep diagnostic work-up should apply either molecular and histological tools to unravel underlying diseases [30].

Until the mid-1990s, the spontaneous endogenous erythroid colonies (EEC) (growth of erythroid colonies in the absence of exogenous erythropoietin) assay was employed as a diagnostic tool to recognize MPN at overt and early stages; in the seminal studies, the EEC assay was positive in 78% of idiopathic BCS [31]. However, this assay requires special technical facilities and lacks standardization, with a specificity of less than 80% [28, 32].

In the last decade, the capacity of diagnosing Philadelphia-negative MPN has been dramatically improved due to the knowledge of the somatic mutations associated with MPN [6–8]. Almost all patients with PV harbor the somatic activating mutation JAK2 V617F in the exon 14 (approximately 96%) or additional mutations in the JAK2 exon 12 (approximately 3%). JAK2 V617F also occurs in ET and PMF, with mutational frequencies of 55% and 65%, respectively. CALR is a multifunctional calcium-binding protein mostly localized in the endoplasmic reticulum. CALR mutations are rare in PV but are present in 25–35% of PMF patients and 15–24% of ET patients. Mutations in the MPL gene are present in approximately 4% of ET patients, 8% of PMF patients, and rarely in PV [7, 8].

6.3.1 JAK2 V617F Mutation

In the meta-analysis mentioned above conducted by Qi et al. [20] on 555 patients with BCS, the pooled prevalence of JAK2 V617F mutation was 43.8% in the patients with a complete diagnostic work-up for MPN. However, the rate of the mutation was as high as 80.5% in the patients who fulfilled the WHO diagnostic criteria for MPN, and 26.6% in the patients who did not [20] (Table 6.1).

Consistently, in the meta-analysis conducted by Smalberg et al. [21], the JAK2 V617F mutation was positive in 42.7% of the BCS patients, 87.2% in those with overt MPN, and 13.6% in those without typical hematologic features of MPN

(Table 6.1). However, the negative predictive value of the JAK2 V617F marker for diagnosis of MPN is low, being the mutation absent in approximately 40% of ET or PMF patients.

The JAK2 V617F mutation is rare in Chinese patients with BCS, suggesting a difference in the causes of BCS between Western countries and China [33–36]. A membranous web that obstructs the terminal portion of the inferior vena cava is rarely present in BCS patients from the Western countries but underlies many cases in Oriental countries. There is evidence that the occluding membranous webs are not congenital, but are due to late sequelae of a previous thrombotic obstruction of the inferior vena cava [37]. Therefore, the role of JAK2 V617F as a diagnostic tool in this setting can be strongly downsized in Oriental countries.

Currently, the JAK2 V617F mutation is widely applied in the diagnostic work-up of patients with BCS and more in general with SVT [24–27]; in contrast, the JAK2 V617F mutation is present in less than 1% of the non-MPN patients with VTE of the common sites, confirming a strong site-linked specificity of JAK2 V617F-related thrombosis [38].

There is evidence that JAK2 V617F can be present not only in blood cells but also in endothelial cells from JAK2 V617F-positive MPN patients, and that the endothelium of splanchnic vessels harbors the JAK2 V617F mutation [39–41]. In vitro model of human endothelial cells overexpressing JAK2 V617F and an in vivo model of mice with endothelial-specific JAK2 V617F expression showed that JAK2 V617F-expressing endothelial cells have a proadhesive phenotype associated with increased endothelial P-selectin and von Willebrand factor exposure secondary to degranulation of Weibel–Palade bodies, and that the murine model displayed a higher propensity for thrombus [42, 43]. Notably, the presence of bone marrow JAK2 V617F-positive endothelial colony-forming cells has been documented either in BCS patients with JAK2 V617F-positive overt MPN and in BCS JAK2 V617F-positive patients without overt MPN [44].

6.3.2 CALR Mutations

The prevalence of the CALR exon 9 mutations in patients with BCS and EHPVO has been recently reviewed [45]. The data of 1492 patients with SVT reported in 11 papers were analyzed; 580 of them had BCS. The pooled proportion of CALR mutations was 1.21% in all SVT patients regardless of JAK2 V16F mutation and MPN status, and the pooled proportion of CALR mutations was 1.41% and 1.59% in BCS and EHPVO patients, respectively. The pooled proportion of CALR mutations in SVT, BCS, and EHPVO patients without JAK2 V617F mutation was 1.52%, 1.03%, and 1.82%, respectively. Accordingly, regular screening for CALR mutations in unselected SVT patients might be of little use. Another finding was that the prevalence of CALR mutations was relatively higher in SVT, BCS, and EHPVO patients with MPN than in those without MPN (SVT: 3.71% vs. 1.21%; BCS: 2.79% vs. 1.41%; EHPVO: 7.87% vs. 1.59%), but the absolute value remained low. By comparison, the prevalence of CALR mutations was remarkably increased in SVT,

BCS, and EHPVO patients with overt MPN after excluding JAK2 V617F mutation (15.16%, 17.22%, and 31.44%, respectively). This phenomenon is consistent with a finding that the CALR and JAK2 V617F mutations are mutually exclusive in the general population of patients with MPN.

6.3.3 MPL Exon 10 and JAK2 Exon 12 Mutations

In their survey of 241 SVT patients (104 with BCS), Kiladjian et al. screened the MPL exon 10 in 212 patients and the JAK2 exon 12 mutations in 123 JAK2 V617F-negative patients; no mutation was found in any patient [32]. Similar results were reported in a series of 66 BCS patients [46]. Moreover, Fiorini et al. [47] did not find any JAK2 exon 12 mutations in 52 SVT patients (7 with BCS). In a series of 93 SVT patients analyzed by Bergamaschi et al. [48], none of the 20 patients with BCS had the MPL or JAK2 exon 12 mutations.

6.3.4 JAK2 46/1 Haplotype

The germline JAK2 46/1 haplotype is strongly associated with the JAK2 V617F somatic mutation; however, the presence of this haplotype is associated with MPN, independently of the presence of the JAK2 V617F mutation [49–51]. In a case-control study on 90 SVT patients without MPN and without the JAK2 V617F mutation and 181 healthy controls, the C allele tagged the 46/1 genotype; the frequency of the CC homozygous genotype was significantly higher in SVT patients than in controls (11.1% vs. 2.8%, odds ratio (OR) 4.4, 95% CI 1.5–13.3). However, no patient with BCS carried the CC genotype [52]. Smalberg et al. [53] investigated 199 patients with SVT and 100 healthy controls. Overall, the C allele frequency was higher in the JAK2 V617F-positive BCS patients (43%, $p = 0.01$) and EHPVO patients (40%, $p = 0.1$) than in the controls (27%); in contrast, the C allele frequency was similar to that of the controls either in the JAK2 V617F-negative BCS and EHPVO patients (33% and 24%, respectively).

A meta-analysis included 26 studies with 8561 cases and 7434 controls; the JAK2 46/1 haplotype resulted independently associated with MPN and SVT. This analysis also suggests an association between the 46/1 haplotype and the occurrence of JAK2 V617F-positive SVT, whereas no association was found in the V617F-negative SVT patients [54]. In conclusion, the 46/1 haplotype seems to be a susceptibility factor for the JAK2 V617F mutation rather than an independent risk factor for SVT.

6.3.5 TET2 Mutations

Precise regulation of DNA methylation patterns is partly mediated by ten-eleven translocation (TET) enzymes and provides fundamental protection against cellular transformation. Thus, TET2 protein is thought to act as a tumor suppressor. The

TET2 gene is mutated in various myeloid malignancies, including in 15% of MPN [55]. A TET2 mutation was found in 8 of 43 BCS patients: of the 6 patients with a deleterious TET2 mutation, two had an overt MPN, and 3 carried both TET2 and JAK2 mutations. In summary, in this cohort a TET2 mutation as a unique molecular marker of MPN was identified in 7% of BCS patients (3/43) [46].

6.4 Diagnostic Strategy

Investigation of the JAK2 V617F mutation and a complete laboratory work-up for thrombophilia is mandatory in patients with non-cirrhotic and non-malignant BCS. Bone marrow biopsy is recommended in SVT patients. This procedure aims to refine the diagnosis of MPN according to the WHO criteria in the patients JAK2 V617-positive and to capture additional cases of MPN in the JAK2 V617F-negative patients [27, 30, 32, 56]. In those latter, a complete molecular work-up including CALR, MPL, and exon 12 mutation should be reserved only for those with bone marrow biopsy highly suggestive of MPN.

6.5 Follow-Up and Long-Term Treatment

6.5.1 Treatment at Diagnosis

In the acute phase, the treatment of patients with BCS and with Philadelphia-negative MPN does not differ from that of patients without MPN. A prompt treatment with low molecular or unfractionated heparin followed by vitamin K antagonists (VKA) should start promptly. A step-wise approach is suggested. In the case of clinical deterioration despite anticoagulation, a second-line based on invasive procedures, such as angioplasty with or without stenting, transjugular intrahepatic portosystemic shunt (TIPS), or surgical portosystemic shunt, should be considered [24, 25, 27]. Systemic thrombolytic therapy with tissue plasminogen activator is scarcely effective, whereas catheter-directed thrombolysis may be useful for the treatment of acute and partially occlusive thrombosis [57–59].

Recently TIPS has been proposed as the treatment of choice for patients with BCS with signs of portal hypertension. Angioplasty/stenting should be the second-line treatment in the subgroup of patients if TIPS is ineffective or unsuitable. Surgical shunts should be the treatment of choice when both TIPS and angioplasty/stenting are ineffective or unsuitable [60]. Liver transplantation should be considered as a salvage treatment [24, 25, 27, 60].

6.5.2 Prognosis

The prognosis of BCS has significantly improved with time [61]. In a small recent series of 27 patients (17 with MPN) all of them were anticoagulated with warfarin or low-molecular-weight heparin. A total of 25 (92.6%) patients also had

primary radiological interventions, consisting of TIPS and/or angioplasty/stenting. The overall survival was 96% at 1 year and 81% at 5 years; no patient required liver transplantation. Therefore an approach of aggressive anticoagulation and early radiological intervention resulted in an excellent medium-term outcome [62].

The impact of a diagnosis of MPN on the survival of SVT patients has been investigated in several studies. Among 832 SVT patients included in a single-center retrospective study the site of thrombosis was as follows: isolated EHPVO in 329 patients, isolated mesenteric vein thrombosis in 76, isolated splenic vein thrombosis in 62, isolated BCS in 45, multi-segment thrombosis in 320. In the multivariate analysis, MPN was an independent predictor of mortality (HR 1.92, 95% CI 1.41–2.61); in this patient series, active cancer and liver cirrhosis were not excluded from the study [63].

In a multicenter prospective cohort of 604 consecutive patients with SVT, 49 had MPN. In those latter the mortality rate was 3.4% patient-years during the 2-year prospective observation, resulting much lower than the mortality rate recorded in patients with liver cirrhosis (16.8%) and solid cancer (39.5%), and slightly higher than the mortality rate recorded in patients with unprovoked SVT (2.3%) or associated with transient risk factors (2.5%) [64].

In a large series of 104 BCS patients with a median follow-up of 3.9 years, overall survival did not differ according to the presence or absence of JAK2 V617F ($p = 0.29$) or of diagnosis of MPN ($p = 0.961$). However, event-free survival was shorter in patients with JAK2 V617F ($p = 0.07$) and significantly reduced in those with MPN ($p = 0.0145$) [32].

6.5.3 Long-Term Antithrombotic Treatment

The introduction in the 1980s of systematic use of VKA in patients with BCS has coincided with a better prognosis [65, 66], although the benefit of oral anticoagulation on the survival of the most severe patients is uncertain [67]. The optimal duration of VKA is unknown, but in general life-long treatment is suggested for BCS [24–27].

A large survey of 163 patients, the majority (86%) receiving VKA, shows that only 5 (8%) developed non-fatal variceal bleeding [68]. In another study on patients with BCS who underwent liver transplantation and received after that VKA, the rate of both recurrent thrombosis and bleeding complications is 11%, but the mortality rate related to recurrence is higher than that related to bleeding (4.4% and 0.8% of patients, respectively) [69].

Specific data on the efficacy and safety of VKA treatment in patients with MPN-related BCS are scarce, and most data are referred to SVT as a whole. In the aforementioned multicenter prospective cohort of 604 patients with SVT (55 with BCS), 49 of them had MPN and showed a 9-fold increased risk of recurrent thrombosis during follow-up [64].

In a series of 36 BCS patients with recurrent thrombosis after liver transplant in 42% of cases (15/36), the presence of a JAK2 mutation was significantly associated

with liver-related thrombotic complications. JAK2 V617F occurred in 11 of the 12 patients who developed post-transplant thrombotic complications and in 10 of the 24 patients who did not ($p < 0.005$). In addition, a JAK2 mutation was associated with an increased risk of thrombosis at any site (14/15 vs. 7/21, $p < 0.005$). An overt MPN was associated with liver-related thrombotic complications (9/12 vs. 8/24, $p < 0.03$) [46].

A retrospective study investigated 181 patients with MPN who presented a first episode of SVT. BCS and EHPVO were diagnosed in 31 (17.1%) and 109 (60.3%) patients, respectively; isolated thrombosis of the mesenteric or splenic veins was detected in 18 and 23 cases, respectively. After this index event, the patients were followed for 735 patient-years and experienced 31 recurrences corresponding to an incidence rate of 4.2 per 100 patient-years. VKAs were prescribed in 85% of patients, and the recurrence rate was 3.9 per 100 patient-years, whereas in the small fraction (15%) not receiving VKA more recurrences (7.2 per 100 patient-years) were reported. Patients with BCS had an incidence rate of new events of 8.0 per 100 patient-years (95% CI 4.0–14.4) that was significantly higher than in those with thrombosis of the portal or other abdominal sites (3.3 per 100 patient-years, 95% CI 2.0–5.1). This difference was due to an increased rate of venous events in BCS patients, whereas no difference between the two groups was noticed in the rate of new arterial thromboses; of note, in patients with BCS there was a 3-fold increase in risk of recurrent SVT in respect to that of patients with other index SVT (5/31, 16.1% vs. 9/150, 6%, OR 3.01, 95% CI 0.93–9.71, $p = 0.06$) [70].

A survey on the use of direct oral anticoagulants in 94 patients with SVT included 9 patients with BCS (4 without and 5 with liver cirrhosis) but did not provide any notice about the occurrence of MPN as the underlying cause of SVT [71]. The use of the direct factor Xa oral inhibitor rivaroxaban has been anecdotally reported in a patient with PV and BCS [29].

6.5.4 Cytoreductive Treatment

In MPN patients with previous thrombosis, cytoreduction is warranted [72]. Whether it is justified to give cytoreduction to SVT patients with JAK2 V617F but without an overt diagnosis of MPN according to the WHO criteria is unexplored. Approximately half of JAK2 V617F–positive SVT patients will not develop MPN during the follow-up [38]; therefore, given the absence of evidence, caution is due in prescribing cytoreductive regimens to such individual. On the other hand, the JAK2 V617F mutation is a risk factor for recurrent thrombosis both in overall SVT patients [73, 74] and in BCS patients having received liver transplantation [46]. Therefore, the use of drugs aimed at reducing the growth of the mutant clone appears reasonable.

In a small retrospective cohort of 17 MPN patients with BCS, all received hydroxyurea and aspirin after liver transplantation, and only one had a recurrent EHPVO [75]. In another small series of 18 MPN patients with BCS, the rate of recurrence was 22% (4/18); all the new thrombotic events occurred in patients who were not receiving cytoreductive treatment [76].

In a pooled cohort of 1500 patients with MPN and thrombosis, the multivariable analysis limited to the patients with first arterial thrombosis showed that recurrent arterial thrombosis was prevented by antiplatelet agents (HR 0.49, 95% CI 0.31–0.78, $p = 0.003$) and by hydroxyurea (HR 0.64, 95% CI 0.42–0.98, $p = 0.04$) and only partially by VKA (HR 0.53, 95% CI 0.27–1.04, $p = 0.06$); on the contrary, in patients with the first venous thrombosis, the venous recurrences were more prevented by VKA (HR 0.57, 95% CI 0.35–0.94) than by antiplatelet agents (HR 0.71, 95% CI 0.41–1.24, $p = 0.24$) or hydroxyurea (HR 0.75, 95% CI 0.46–1.23, $p = 0.26$). Notably, analyzing patients with VTE according to the site of thrombosis, hydroxyurea was confirmed to be without a significant effect on the rate of either recurrent thrombosis or recurrent VTE in 218 patients with SVT (38 with BCS) (HR 0.81, 95% CI 0.39–1.65, $p = 0.56$, and HR 0.92, 95% CI 0.40–2.13, $p = 0.85$, respectively), after adjustment for age, sex, antiplatelet treatment, VKA treatment, and cytoreductive agents other than hydroxyurea [19]. The reason for this finding is difficult to explain; it could be speculated that in patients with SVT hypercytemia is less frequent [28] so that cytoreduction in this setting could be less crucial than otherwise.

6.5.5 Orthotopic Liver Transplantation

Failure of the interventions mentioned above occurs in 10–20% of patients with BCS, who are therefore candidates for orthotopic liver transplantation [77].

In a series of 36 BCS patients, the 1-year and 5-year survival rates after liver transplantation were 84% and 69%, respectively; the presence of a molecular hallmark for MPN did not influence the survival rate [46]. In another series of 25 BCS patients, the mortality rate after liver transplantation was similar in MPN patients (3/18, 16.7%) and non-MPN patients (1/7, 14.3%) [76].

In a retrospective cohort of 78 BCS patients, the long-term survival after liver transplantation was similar in MPN patients ($n = 41$) and non-MPN patients ($n = 37$): the 5-year survival was 78% vs. 76%, respectively, $p = 0.81$, and the 10-year survival was 68% vs. 73%, respectively, $p = 0.66$. Twelve of the 41 MPN patients (29%) died within the first 3 years after liver transplantation, but death was related to the hematologic disease only in one case with recurrent BCS [78].

In two series of BCS patients, no progression to myelofibrosis or acute leukemia was observed after liver transplantation in 17 patients with a follow-up up to 20 years [75] and in 78 patients with a mean follow-up time of 12.4 years (range 3–28.4 years) [78].

6.6 Conclusions

The strong association between MPN and BCS is well established. The knowledge of the molecular mutations underlying MPN has dramatically improved in the last decade, allowing early diagnosis of MPN in a significant portion of BCS patients.

The JAK2 V617F mutation has a thrombotic potential much more increased than the other molecular diagnostic-drivers both in patients with and without an overt diagnosis of MPN.

Aggressive treatment of BCS with anticoagulation and early endovascular treatment improved the prognosis irrespective of the presence of MPN. The standard-of-care for long-term antithrombotic treatment is based on VKA, and data about efficacy and safety of direct oral anticoagulants are urgently needed. The impact of cytoreduction with hydroxyurea has been reported to be effective in preventing recurrent thrombosis in small series of patients with BCS, but the appropriateness of using antiproliferative drugs in patients with uncertain progression to overt forms of MPN remains to be established. Moreover, the efficacy of hydroxyurea in preventing recurrent VTE in MPN patients has been recently questioned, in particular in those with SVT.

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