Ruxolitinib for treatment of polycythemia vera and myelofibrosis in patients after liver transplantation

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Key clinical message:
Ruxolitinib seems a feasible treatment strategy for patients with polycythemia vera or myelofibrosis after liver transplantation.

Abbreviations

bid	bis in die, twice daily
CNI	calcineurin inhibitor
CRP	C-reactive protein
CT	Computed tomography
MF	myelofibrosis
MPD	myeloproliferative disease
MRI	Magnetic resonance imaging
PV	polycythemia vera
Ref Range	Laboratory reference range
VCI	inferior vena cava

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Abstract

Patients after liver transplantation have an increased risk to develop haematologic neoplasias. Information how to treat these patients in the context of immunosuppression is sparse. Here, we report two patients with polycythemia vera (PV) and myelofibrosis (MF) on ruxolitinib after liver transplantation.

Introduction

Ruxolitinib (Jakavi®), an inhibitor of Janus-kinase 1 and 2, enables efficient therapy of myeloproliferative disease such as polycythemia vera

(PV) and myelofibrosis (MF) by reducing spleen size and constitutional symptoms. However, ruxolitinib is a potent immunosuppressor and thus might contribute to the high risk of infectious complications due to long-term immunosuppression after liver transplantation [1]. Clinical information on outcomes and risks of ruxolitinib therapy after liver transplantation is limited, although myeloproliferative neoplasms after liver transplantation have been described in some cases [2].

Here, we report on two patients who developed progressive myeloproliferative disease after liver transplantation and therefore were treated with ruxolitinib.

Patient 1

Ten years after liver transplantation for acute liver failure of unknown origin, a 49-year-old female patient on mycophenolic acid (3x360 mg/day) and tacrolimus (1,5 mg/day) developed JAK2 V617F positive polycythemia vera. PV was at first treated with acetylsalicylic acid and intermittent phlebotomy. Three years later, platelet counts and hemoglobin levels dropped, and a second bone marrow biopsy confirmed progression to post-PV myelofibrosis. However, being afraid of potential side effects, our patient refused therapy with ruxolitinib and therefore was continued on acetylsalicylic acid alone. Two months later, urinary outflow obstruction was diagnosed by ultrasound, and a surgical pyeloplasty was advised. Again, the patient was afraid of complications and refused surgery, accepting the increased risk to develop urinary tract infections.

Subsequently, her health tremendously deteriorated further: Her enlarged spleen reached a size of 22 cm in length and she became

increasingly weaker so that she was barely able to walk. Finally, she agreed to start treatment with 10 mg bid ruxolitinib. Within the next six months her general health rapidly improved, she gained 22 pounds in weight, spleen size decreased to 17 cm, and platelet counts normalized. Intermittent facial edema and eye redness were the only side effects attributed to ruxolitinib. However, the patient developed bacterial pneumonia, treated successfully with a course of piperacillin/tazobactam for 7 days, and two episodes of cystitis responding well to oral fosfomycin (3 g single shot). Despite the infections, ruxolitinib was continued without interruption, and the patient made a rapid recovery after each infection.

18 months later, the patient developed leukocytosis of 25.8 G /l (ref. range 3.6-10.5 G/l) and erythrocytosis of 6.8 T/l (ref. range 3.85-5.2 G/l). A CT scan of the chest revealed mild residual changes after pneumonia in her basal lung sections, but a meticulous work-up did not provide any evidence to support infection (CRP= 0.6 mg/l, ref. range: 0-3 mg/l). Thus, the leukocytosis was attributed to the haematological malignancy rather than infection. Consequently, the dose of ruxolitinib was increased to 15 mg bid. Blood counts and general health improved immediately once more, so that ruxolitinib has been continued at the higher dose. Since then, the patient experienced five further episodes of cystitis, which rapidly responded to oral antibiotic treatment with either trimethoprim/sulfamethoxazol (960 mg bid for five days) or fosfomycin (3 g single shot), respectively. During the entire post-transplant observation period her immunosuppressive regimen remained unchanged, in particular because the patient was afraid of transplant rejection.

Patient 2

This young female patient had to undergo three liver transplantations because of recurrent thrombotic events. The first transplantation was performed due to Budd-Chiari-Syndrome at the age of 19 years. The second transplantation was needed to treat focal nodular hyperplasia with partial thrombosis of the liver veins at the age of 38. A third transplantation was needed shortly thereafter owing to acute occlusion of the porto-caval anastomosis. Myeloproliferative disease was suspected but was not confirmed over the next 16 years although clinical and lab investigations were done repeatedly. Likewise, an underlying coagulopathy was not detected. In order to prevent further thrombotic complications she received phenprocoumon (target range: INR of 2.5-3). Despite her history with recurrent thromboses the patient continued smoking (14 py, 30 cig/day).

Her initial immunosuppressive medication after liver transplantation comprised ciclosporin and prednisone. 6 years after the first transplant, immunosuppression was changed to tacrolimus (prograf) and mycophenolate which had to be switched to daily sirolimus 1 mg and prednisolone 2,5 mg three years later, because she developed calcineurin inhibitor (CNIs)-induced kidney injury.

Sixteen years after the third transplant, a kidney tumor in the right kidney combined with thrombosis of the inferior vena cava (VCI) was identified during a routine follow-up MRI. The kidney tumor was removed by heminephrectomy and was classified as a 23 mm papillary, moderately differentiated renal cell carcinoma (pT1a, L0, V0, R0, Pn0) by histology. A radiological attempt to re-canalize the VCI closure failed and phenprocoumon was continued (target range: INR of 2.5-3).

Six months later, hemoglobin steadily increased to 19.8 g/dl (Ref. range 12-15.4 g/dl; hematocrit of 58% (Ref. range 35.5-45)). Now, JAK2 V617F positive polycythemia vera was confirmed for the first time by genetic

testing and bone marrow biopsy. Molecular studies identified an ETV6 deletion, and next generation sequencing also showed JAK2-V617F mutation and DNMT3A-S770L mutation in 70% and 40% of cells, respectively. Bone marrow histology revealed moderate reticulin fiber fibrosis and collagen fiber fibrosis (M2).

As a first therapeutic step, her high hematocrit was lowered by phlebotomies. Next, ruxolitinib 15 mg bid was initiated. Progressive pancytopenia developed so that the dose was reduced to 10 mg once daily. At this lower dosage, the patient still had reduced hemoglobin and platelet counts, which however remained stable. Her splenomegaly declined from 20 cm to 14 cm in diameter and the patient reported a good clinical recovery and stable general well-being. Finally, ruxolitinib was given in two divided daily doses of 5 mg, which further improved tolerability. Immunosuppression was continued with daily 1 mg sirolimus and 2.5 mg prednisolone. Thus far, this patient has not suffered from any infectious complications.

Discussion

Malignancies are the most frequent cause of mortality in adult liver transplant recipients [3]. Myeloproliferative neoplasms after liver transplantation have been described, but seem to be rather rare events [2] and underlying haematologic aetiologies may become unmasked only several years after liver transplantation in patients with Budd-Chiari syndrome and thrombotic hepatic diseases, as is illustrated in our second patient. Nevertheless, data on treatment of PV and MF are lacking for patients after liver transplantation. Of note, in a cohort of 17 patients with liver transplantation for Budd-Chiari syndrome, twelve patients (71%) had detectable evidence of an underlying myeloproliverative disorder. These patients were treated with warfarin,

hydroxyurea, and aspirin [4]. Treatment of myeloproliferative neoplasms in patients after organ transplantation is hampered by the fact that the alternative use of interferons would probably induce organ rejection. On the other hand, the long time hydroxyurea promotes the development of secondary malignancies, additive to the risk caused by the long-term immunosuppression for organ transplantation.

There are no known direct interactions between immunosuppressive agents used in liver transplant recipients and ruxolitinib. Nevertheless, an increased risk for infectious complications must be assumed given that ruxolitinib which can be used for the treatment of graft versus host disease, has profound immunosuppressive effects [5]. In the clinical settings it remains unclear, how to adjust long-term immunosuppression after solid organ transplantation when ruxolitinib must be administered.

The randomized, double-blind and placeblo controlled study COMFORT I and II demonstrate that ruxolitinib relieves symptoms and improves survival. Accordingly, in our two patients occurred astonishing improvements in clinical presentation and quality of life after treatment with ruxolitinib was started. However, one of our patients experienced more frequent episodes of cystitis in the context of an anatomic predisposition, and pneumonia as infectious complications under ruxolitinib. In the COMFORT I study, sepsis (2.6%) and pneumonia (1.9%) were the leading adverse events contributing to death in the ruxolitinib arm [6]. Of note, it has been shown that ruxolitinib decreases the function of dendritic cells, NK cells and T cells as important players of immune control [7,8].

There is no data on how immunosuppression in solid-organ recipient should be adjusted in concomitant treatment with ruxolitinib to avoid infectious complications. Given that both ruxolitinib and mycophenolate display strong antiproliferative properties, the increased frequency of

infections in patient 1 may be related to this combination. However, the patient declined to at least reduce the dose of mycophenolate.
Our patients were regularly monitored for any infections and we strongly recommend to follow this strategy when ruxolitinib has to be prescribed after liver transplantation, taking into account published clinical experience is still limited to few patients with rather short observation periods.

Taken together, our patients confirm a positive treatment response of myeloproliferative disease to ruxolitinib, leading to a rapid relief of symptoms and improved quality of life. These clinical observations suggest a favourable balance between risks and benefits in patients after liver transplantation who may need ruxolitinib therapy for severe progressive PV and MF. Thus, we hope that our case series will stimulate more reports on the use of ruxolitinib in solid organ transplantation to establish optimal concomitant immunosuppression regimens and monitoring intervals.

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1. Heine A, Brossart P, Wolf D (2013) Ruxolitinib is a potent immunosuppressive compound: is it time for anti-infective prophylaxis?. *Blood* 122 (23): 3843–3844.

2. Wu B, Ingersoll K, Jug R, Yang LH, Luedke C, Lo A, Su P, Liu X, Rehder C, Gong J, Lu CM, Wang E (2017) Myeloid Neoplasms Following Solid Organ Transplantation: Clinicopathologic Studies of 23 Cases. *Am J Clin Pathol*. Dec 20;149(1):55-66.

3. Fung JJ, Jain A, Kwak EJ, Kusne S, Dvorchik I, Eghtesad B (2001) De novo malignancies after liver transplantation: a major cause of late death. *Liver Transpl*. 7:S109-118.

4. Melear JM, Goldstein RM, Levy MF, Molmenti EP, Cooper B, Netto GJ (2002) Hematologic aspects of liver transplantation for Budd-Chiari syndrome with special reference to myeloproliferative disorders. *Transplantation* 74:1090-1095.

5. Escamilla Gómez V, García-Gutiérrez V, López Corral L (2020) Ruxolitinib in refractory acute and chronic graft-versus-host disease: a multicenter survey study. *Bone Marrow Transplant* 55, 641–648

6. Verstovsek S, Mesa RA, Gotlib J, Gupta V, DiPersio JF, Catalano JV. Long-term treatment with ruxolitinib for patients with myelofibrosis: 5-year update from the randomized, double-blind, placebo-controlled, phase 3 COMFORT-I trial. J Hematol Oncol (2017),10:55.

7. Heine A, Held SA, Daecke SN et al. The JAK-inhibitor ruxolitinib impairs dendritic cell function in vitro and in vivo. Blood (2013) 122 (7): 1192–1202.

8. Schönberg K, Rudolph J, Wolf, D. NK cell modulation by JAK inhibition. Oncoscience (2015) 2(8), 677–678.