CASE REPORT

Ruxolitinib treatment in an infant with JAK2+ polycythaemia vera-associated Budd-Chiari syndrome

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SUMMARY

Budd-Chiari syndrome (BCS) is caused by hepatic venous outflow obstruction commonly seen with myeloproliferative neoplasms (MPNs). Polycythaemia vera (PV) is a very rare MPN in childhood. This is the youngest reported patient diagnosed with PV and BCS secondary to JAK V617F mutation.

A 26-month-old girl was admitted with a 5-month history of abdominal distension, hepatosplenomegaly and ascites. Imaging studies revealed occlusion of the right hepatic vein and marked attenuation of the middle and left hepatic veins. BCS was diagnosed after excluding other causes of chronic liver disease. Mandatory prothrombotic workup revealed underlying PV.

Partial recanalisation of hepatic veins occurred following anticoagulation therapy and PV was well controlled by pegylated interferon and hydroxycarbamide until she developed nephrotic syndrome, likely secondary to pegylated interferon. Therefore, treatment was modified to ruxolitinib, a novel-JAK-2 inhibitor; the therapy has been effective for almost 20 months with a good response and has no side effects.

BACKGROUND

Budd-Chiari syndrome (BCS) is characterised by hepatic venous outflow obstruction with myeloproliferative neoplasms (MPNs) accounting for around 50% of adult patients.¹ Polycythaemia vera (PV) is a very rare MPN in childhood with an estimated prevalence of 2 cases per 10 million persons younger than 20 years.^{2,3} PV is the result of clonal expansion of haematopoietic stem cells.³ The pathogenesis is not fully understood, but is believed to be associated with mutations of the Janus-associated kinase (JAK)-signal gene(s) and signal transducer and activator of transcription pathways, leading to deregulation and enhanced proliferation of haematopoietic progenitor cells.^{4,5} BCS is a common complication of PV in adults and children, particularly in patients with JAK2V617F mutation, which has a 45% prevalence among adult BCS patients.⁶ We present our experience in managing a very young child with this association, with a novel agent.

CASE PRESENTATION

A 26-month-old girl of Indian origin, the first born to non-consanguineous parents, was admitted to our hospital with a 5-month history of abdominal distension. There were no other symptoms such as fever, vomiting, night sweats, appetite or weight

loss. Hepatomegaly and splenomegaly (4 cm and 1 cm below costal margin, respectively) and ascites were detected. Dilated veins on the anterior abdominal wall and the back were noted. Her vital signs and physical examination of other systems were unremarkable.

INVESTIGATIONS

Investigations showed: Aspartate aminotransferase (AST) 71 (10–77 IU/L), bilirubin 13 (<20 µmol/L), alkaline phosphatase (ALP) 117 (129–291 IU/L), gamma-glutamyl transferase (GGT) 26 (<55 IU/L), albumin: 46 (35–50 g/L), total protein: 65 (60–80 g/L), Na: 137 mmol/L, K: 5 mmol/L, urea 3.8 mmol/L, Ca: 2.28 mmol/L, creatinine 24 (45–120 µmol/L), phosphate 1.51 mmol/L, haemoglobin (Hb) 93 g/L, mean corpuscular volume (MCV): 56.8 fl, RBC $5.68 \times 10^{12}/L$, white blood cell WBC $13.0 \times 10^9/L$, platelets: $671 \times 10^9/L$, reticulocytes $128 \times 10^9/L$. Hb high performance liquid chromatography (HPLC) identified Hb D (Punjab) variant (29%), ferritin 5 (20–200 µg/L), serum iron 5 (14–30 µmol/L), total iron binding capacity (TIBC) 84 (50–72 µmol/L) and iron saturation 6% (20%–50%) consistent with iron deficiency, erythropoietin 10.3 (5–25 IU/L). International normalised ratio (INR) 1.35 (0.9–1.2), activated partial thromboplastin ratio 1.3 (0.85–1.15), Clauss fibrinogen 2.6 (1.5–4.5 g/L).

Abdominal ultrasonography scan (USS) showed an enlarged liver and spleen and patent portal vein with normal velocity antegrade flow; the left and middle hepatic veins were patent with low velocity flow, but the right hepatic vein was not identified. Magnetic resonance venography confirmed the occlusion of the right hepatic vein and marked attenuation of the middle and left hepatic veins. Echocardiography demonstrated normal cardiac structure and function with a clinically insignificant pericardial effusion. The diagnosis of BCS was made after excluding other causes of chronic liver disease (alpha-1 antitrypsin deficiency, Wilson's disease, chronic hepatitis B and C and autoimmune liver disease). Thrombophilia testing demonstrated normal activated protein C (APC) resistance-V: 2.0 (normal 2.0–3.0 ratio), protein C: 51 (age-appropriate normal range, 40–92 U/dL), free protein S 90% (normal adult range 60%–150%) and antithrombin: 74 (80–130%)). Genetic analysis of *Factor V Leiden* c.1601G>A, *Prothrombin* G20210A and *MTHFR* mutations showed germline configuration. Paroxysmal nocturnal haemoglobinuria screening for glycosyl phosphatidylinositol (GPI)-deficient

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populations by flow cytometry was negative. Lupus anticoagulant screen diluted Russell's viper venom test (DRVVT) was negative initially but became positive in association with antiphospholipid (cardiolipin) IgG antibodies GPL 50 (<10 IU/L), which were both confirmed 6 weeks later, consistent with antiphospholipid syndrome; anti-nuclear antibody, anti-smooth muscle antibody, and anti-double stranded DNA (anti-dsDNA) were negative. Coeliac disease was excluded by negative anti-tissue transglutaminase at presentation, 0.4 U/mL and, 3 years later 0.8 U/mL (normal <7 U/mL).

Bone marrow aspirate and trephine demonstrated 90% cellularity with hyperplasia of granulopoiesis and particularly erythropoiesis; megakaryocytes were numerous with tight clustering and abnormal forms. The reticulin stain was increased (grade 1–2) and the appearances were those of a MPN, not further classifiable. Cytogenetic analysis showed normal karyotype 46,XX; *JAK2V617F* mutation was detected 22.7% and 27.8% in peripheral blood and bone marrow, respectively; p210 M-BCR-ABL (major breakpoint cluster region and Abelson murine leukemia viral onkogen homolog 1 hybrid gene) (e13a2; e14a2) transcripts were not detected. Parental testing was negative for the *JAK2V617F*.

DIFFERENTIAL DIAGNOSIS

The diagnosis of BCS was made after excluding other causes of chronic liver disease (alpha-1 antitrypsin deficiency, Wilson's disease, chronic hepatitis B and C and autoimmune liver disease).

TREATMENT

The patient was treated with spironolactone (4 mg/kg/day), chlorothiazide (5 mg/kg/day), low-molecular-weight heparin (LMWH)—dalteparin (100 IU/kg/day), vitamin K (1 mg/day) and intermittent 20% albumin (5 mL/kg) infusions with paracentesis for the control of ascites. LMWH was converted to long-term oral anticoagulation with warfarin, while low-dose aspirin was added as the platelet count increased to $946 \times 10^9/L$. The iron deficiency and microcytic anaemia at presentation were treated with oral iron supplements (5 mg/kg/day), but Hb rose rapidly to 147 g/L and the platelets to $2202 \times 10^9/L$, unmasking the underlying myeloproliferative state. Initial cytoreduction was achieved with hydroxyurea (hydroxycarbamide 15 mg/kg/day); this was withdrawn following introduction of weekly subcutaneous pegylated interferon alpha-2a (45 µg), with clinical, haematological and molecular response. Abdominal distension resolved after 10 days and full recanalisation of the right hepatic vein was observed within 2 months. The thrombocytosis resolved and the *JAK2*-mutated clone decreased to 4% and declined further during the second treatment year.

OUTCOME AND FOLLOW-UP

Elective oesophagogastroscope at 6 months did not identify signs of portal hypertension. Following an episode of melaena and acute anaemia at 11 months from diagnosis, an emergency endoscopy could not identify a bleeding source, but the aspirin was stopped. Haematopoietic stem cell transplantation (HSCT) was considered, but there was no suitable donor and her clinical condition was deemed relatively stable on medical management.

After 2 years of pegylated interferon treatment, the patient developed abdominal distension and oliguria, with no peripheral oedema or hypertension, high urine protein/creatinine ratio (3715 mg/mmol) and low serum albumin, leading to clinical diagnosis of nephrotic syndrome. Renal biopsy was precluded

due to risk of the bleeding, and she was treated with oral steroids without response. After 5 weeks, pegylated interferon was stopped with clinical improvement. Haematological control was maintained with hydroxycarbamide, but in view of her young age, this was not considered an optimal long-term treatment. Three years from diagnosis, ruxolitinib (Jakavi, Novartis), a novel *JAK-2* inhibitor licensed in adults, was supplied by Novartis for compassionate use; the starting dose of 5 mg BD (twice a day) was gradually increased to 25 mg BD, while continuing hydroxycarbamide. The new medication was well tolerated with no apparent side effects, infections or cytopenias requiring treatment interruption. The patient has shown a partial response, with reduction in spleen size (from 4 cm below the costal margin (USS length 12.3 cm) to non-palpable (USS length 10.2 cm)) after 2 months and she continued on maintenance treatment including ruxolitinib, hydroxycarbamide, warfarin, spironolactone and iron. The most recent blood analysis, 60 months after presentation and 20 months after ruxolitinib was initiated, showed: WCC: $6.8 \times 10^9/L$, Hb: 112 g/L, MCV: 85 fl, PLT $514 \times 10^9/L$, reticulocytes $58 \times 10^9/L$, INR 2.5, albumin: 48 g/L, bilirubin 11 µmol/L, GGT 77 IU/L, AST 48 IU/L, ALP 375 IU/L; she has persistent antiphospholipid antibodies but there have been no further thrombotic events. Additionally, her *JAK2* allele burden remains stable at 22% and the most recent USS, nearly 5 years from presentation, demonstrated patency of all hepatic veins and the spleen length was 10.3 cm. Her growth, which had faltered on pegylated interferon has resumed. She has not experienced any serious systemic infections and ruxolitinib has been generally well tolerated.

DISCUSSION

This is the youngest reported patient diagnosed with PV and BCS secondary to *JAKV617F* mutation. PV is very rare in childhood and the *JAKV617F* mutation appears to be less prevalent among children with PV compared with adults (25% and 90%–95%, respectively).^{3 7 8}

The standard treatment for BCS due to PV is long-term anticoagulation combined with invasive radiological interventions or liver transplantation.¹ Because of her exceptionally young age and small size, our patient was treated medically with anticoagulation and cytoreduction. Myeloproliferative disease (MPD) should always be considered in patients presenting with BCS and full procoagulant screening including genetic analysis for *JAK2V617F* mutation, which is commonly detected in adult patients with PV, is mandatory. Furthermore, *JAK2*-negative adults with PV should be additionally tested for *JAK2* exon 12 mutations, as activation of *JAK2* signalling plays an important role in pathogenesis of PV.^{8 9} At presentation, our patient was anaemic due to coexisting iron deficiency anaemia and an Hb variant; treatment of the iron deficiency unmasked the underlying PV. In BCS, the presence of anaemia should not preclude investigation for MPDs, since if undetected, this could exacerbate the BCS symptoms and lead to further thrombotic or bleeding events and longer term, haematological clonal evolution. Similarly, thrombocytosis or leucocytosis may not be evident at presentation, leading to the MPD being overlooked.

The identification and treatment of the underlying cause in BCS is necessary to control the disease. The rarity of PV in children results in very limited data on which to base recommendations; treatment approaches are generally drawn from experience in adults, including phlebotomy or erythrocytapheresis, with or without hydroxycarbamide¹⁰ or interferon. The available treatments may have important toxicities in children; interferon

can be associated with pancytopenia, psychiatric disorders and autoimmune phenomena, while the European LeukemiaNet recommends caution when treating children with hydroxycarbamide due to the possible long-term risks of leukemogenicity in those with myeloproliferative disorders¹¹; PV has an inherent long-term risk of progression to myelofibrosis or acute myeloid leukaemia in adults.¹²

HSCT is the only curative treatment for PV, and there are only two case reports in children, a 14-year-old girl treated with phlebotomy and hydroxyurea for 34 months who underwent sibling-matched allogeneic HSCT as her clinical condition deteriorated,¹³ and a 9-year-old boy with PV managed with phlebotomy for 27 months who developed thrombocytosis and was treated with interferon-alpha. Despite effective control of his blood count, he developed progressive splenomegaly, raising concerns about MPD progression and he underwent (human leukocyte antigen)HLA-matched unrelated donor HSCT.¹⁴

Interferons have been used in treatment of MPNs, including PV, for almost 40 years, but the high prevalence of side effects have limited their clinical application.¹⁵ The novel pegylated form of interferon has advantages of longer half-life, better stability, less immunogenicity and improved tolerance.¹⁶ Phase II and III studies of pegylated interferon alfa-2a for treatment of PV in adults have shown promising results,^{17,18} with reduction in the *JAK2* allele burden as seen in our patient, as well as molecular and clinical remission. Successful interferon treatment has been reported in children with PV.^{19–21} Therefore, because of her age and lack of a matched HSCT donor, our patient was started on pegylated interferon alfa-2a (initially with hydroxycarbamide due to extreme thrombocytosis), leading to good disease control for 2 years until development of steroid-resistant nephrotic syndrome. A mild, reversible proteinuria is common during interferon therapy, but nephrotic syndrome has been reported rarely on pegylated interferon.^{22–24} It is usually observed during initial weeks or months of treatment and rarely as late as in our patient.²⁵ Renal function usually recovers after the withdrawal, but this is not universal.²⁴

Ruxolitinib is a novel *JAK2* inhibitor, which inhibits growth of erythroid and myeloid progenitor cells with the *JAK2V617F* mutation in patients with PV.⁹ The drug is approved by the US Food and Drug Administration for treatment of adult PV patients with an inadequate response to/or intolerant of hydroxycarbamide, after the demonstration of clinical benefit in phase II and III studies,^{26,27} particularly in patients with persisting splenomegaly.²⁸ Anaemia and thrombocytopaenia were the most common haematological adverse events associated with ruxolitinib,²⁶ requiring dose reduction or interruption of treatment.

Ruxolitinib has been evaluated in a phase I dosing study in children with relapsed or refractory solid tumours and leukaemias and included one child with PV who had a partial response after 28 days, but had to be discontinued after 504 days following disease progression.²⁹

In our limited experience, ruxolitinib has been well tolerated in PV treatment during 20-month follow-up and has been associated with stable disease, resolution of splenomegaly and should be considered in children with PV and BCS who cannot tolerate interferon. If its efficacy and safety record is further documented it may reduce the need for consideration of HSCT in *JAK2* mutation-related cases of PV-associated BCS in the future.

Contributors MEC: acquisition of data, planning the layout and drafting case report (article), also making necessary changes after revisions. SH: primary diagnosis, treatment and follow-up of the patient and revising the draft critically for important intellectual content. AD: primary diagnosis, treatment and follow-up of the patient, also final approval of the report. NH: primary diagnosis, treatment and follow-up

Learning points

- ▶ Myeloproliferative disease (MPD) should always be considered in patients presenting with Budd-Chiari syndrome (BCS); a full procoagulant screening including genetic analysis for *JAK2V617F* mutation and exon 12 mutations in patients who are *JAK2*-negative is mandatory.
- ▶ In BCS, the presence of anaemia should not preclude investigation for a myeloproliferative disorder, since this may be masked by coexistent iron deficiency and lead to further thrombotic or bleeding events and haematological clonal evolution longer term.
- ▶ Novel therapeutic agents may reduce the need for haematopoietic stem cell transplantation in *JAK2* mutation-related cases of polycythaemia vera-associated BCS in the future.

of the patient, planning the content and layout of the case report, also revising the draft critically for important intellectual content. NH and SH are the ones responsible for the overall content as guarantors.

Competing interests None declared.

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REFERENCES

- Goel RM, Johnston EL, Patel KV, et al. Budd-Chiari syndrome: investigation, treatment and outcomes. *Postgrad Med J* 2015;91:692–7.
- McNally RJ, Rowland D, Roman E, et al. Age and sex distributions of hematological malignancies in the U.K. *Hematol Oncol* 1997;15:173–89.
- Cario H, McMullin MF, Pahl HL. Clinical and hematological presentation of children and adolescents with polycythemia vera. *Ann Hematol* 2009;88:713–9.
- Barbui T, Finazzi G, Falanga A. Myeloproliferative neoplasms and thrombosis. *Blood* 2013;122:2176–84.
- Quintás-Cardama A, Verstovsek S. Molecular pathways: jak/STAT pathway: mutations, inhibitors, and resistance. *Clin Cancer Res* 2013;19:1933–40.
- Barbui T. How to manage children and young adults with myeloproliferative neoplasms. *Leukemia* 2012;26:1452–7.
- Ismael O, Shimada A, Hama A, et al. Mutations profile of polycythemia vera and essential thrombocythemia among Japanese children. *Pediatr Blood Cancer* 2012;59:530–5.
- Hofmann I. Myeloproliferative neoplasms in Children. *J Hematop* 2015;8:143–57.
- McKeage K. Ruxolitinib: a Review in Polycythemia Vera. *Drugs* 2015;75:1773–81.
- Giona F, Teofili L, Moleti ML, et al. Thrombocythemia and Polycythemia in patients younger than 20 years at diagnosis: clinical and biologic features, treatment, and long-term outcome. *Blood* 2012;119:2219–27.
- Barbui T, Barosi G, Birgegard G, et al. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. *J Clin Oncol* 2011;29:761–70.
- Harrison CN, Bareford D, Butt N, et al. Guideline for investigation and management of adults and children presenting with a thrombocytosis. *Br J Haematol* 2010;149:352–75.
- Reinhardt H, Klingebiel T, Lang P, et al. Stem cell transplantation for polycythemia vera. *Pediatr Blood Cancer* 2008;50:124–6.
- Stobart K, Rogers PC. Allogeneic bone marrow transplantation for an adolescent with polycythemia vera. *Bone Marrow Transplant* 1994;13:p. 337–339.
- Falchi L, Newberry KJ, Verstovsek S. New therapeutic approaches in Polycythemia Vera. *Clin Lymphoma Myeloma Leuk* 2015;15 Suppl:S27–S33.
- Veronese FM, Mero A. The impact of PEGylation on biological therapies. *BioDrugs* 2008;22:315–29.
- Kiladjian JJ, Cassinat B, Chevret S, et al. Pegylated interferon-alfa-2a induces complete hematologic and molecular responses with low toxicity in polycythemia vera. *Blood* 2008;112:3065–72.
- Quintás-Cardama A, Kantarjian H, Manshouri T, et al. Pegylated interferon alfa-2a yields high rates of hematologic and molecular response in patients with advanced essential thrombocythemia and polycythemia vera. *J Clin Oncol* 2009;27:5418–24.
- Nagy K, Hunyadi K, Feher I, et al. [Polycythemia vera in an 11-year old girl]. *Orvosi hetilap* 1996;137:p. 27–30.

- 20 Olpinski M, Jakiela T, Korczowski R. [Interferon alpha in the treatment of polycythemia vera in a 13-year-old girl]. *Pediatr Pol* 1996;71:p. 705–7.
- 21 Cario H, Schwarz K, Herter JM, *et al*. Clinical and molecular characterisation of a prospectively collected cohort of children and adolescents with polycythemia vera. *Br J Haematol* 2008;142:622–6.
- 22 Jones GJ, Itri LM. Safety and tolerance of recombinant interferon alfa-2a (Roferon-A) in Cancer patients. *Cancer* 1986;57:1709–15.
- 23 Quesada JR, Talpaz M, Rios A, *et al*. Clinical toxicity of interferons in Cancer patients: a review. *J Clin Oncol* 1986;4:234–43.
- 24 Alves Couto C, Costa Faria L, Dias Ribeiro D, *et al*. Life-threatening thrombocytopenia and nephrotic syndrome due to focal segmental glomerulosclerosis associated with pegylated interferon alpha-2b and Ribavirin treatment for hepatitis C. *Liver Int* 2006;26:1294–7.
- 25 Lederer E, Truong L. Unusual glomerular lesion in a patient receiving long-term interferon alpha. *Am J Kidney Dis* 1992;20:516–8.
- 26 Verstovsek S, Passamonti F, Rambaldi A, *et al*. A phase 2 study of ruxolitinib, an oral JAK1 and JAK2 inhibitor, in patients with advanced polycythemia vera who are refractory or intolerant to hydroxyurea. *Cancer* 2014;120:513–20.
- 27 Verstovsek S, Kiladjian JJ, Griesshammer M, *et al*. Results of a prospective, randomized, open-label phase 3 study of ruxolitinib (RUX) in polycythemia vera (PV) patients resistant to or intolerant of hydroxyurea (HU): the RESPONSE trial. *Journal of Clinical Oncology* 2014;32.
- 28 Bryan JC, Verstovsek S. Overcoming treatment challenges in myelofibrosis and polycythemia vera: the role of ruxolitinib. *Cancer Chemother Pharmacol* 2016;77:1125–42.
- 29 Loh ML, Tasian SK, Rabin KR, *et al*. A phase 1 dosing study of ruxolitinib in children with relapsed or refractory solid tumors, leukemias, or myeloproliferative neoplasms: a Children's Oncology Group phase 1 consortium study (ADVL1011). *Pediatr Blood Cancer* 2015;62:1717–24.

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