Case Report

Treatment of Hepatitis C in a Case of Pediatric B-Cell Acute Leukemia

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Abstract

The prevalence of hepatitis C virus (HCV) infection in Pediatric patients with lymphoproliferative diseases has most commonly been reported with B cell Non-Hodgkin lymphoma. Case studies have reported the requirement of dose reduction or suspension of chemotherapy in 80% of Pediatric ALL cases who are anti-HCV positive owing to hepatotoxicity. The standard of care anti HCV therapy in children aged 3-17 years had been peginterferon and ribavirin for 48 weeks. FDA approved pan-genotypic, anti- HCV regimen, sofosbuvir/velpatasvir [SOF/VEL], for the Pediatric population >6yrs of age or >17 kg body weight in March 2020. We herein report a case of an HCV infected Pediatric B cell ALL patient who was treated with SOF/VEL concomitantly with an intensive chemotherapy regimen. Child tolerated the full dose chemotherapy along with antivirals for 12 weeks and was in morphological remission with sustained virological response.

Keywords: Acute leukemia, direct-acting antiviral, hepatitis C virus, pediatric

Introduction

Hepatitis C virus infection (HCV) has been recognized globally as a public health crisis, with above 70 million individuals found infected with HCV in 2015 and around 400,000 deaths occurring per year worldwide, as reported by the World Health Organization (WHO).[1] The natural history of HCV infection is more aggressive in patients with hematological malignancies because of the simultaneous administration of cytotoxic chemotherapy,[2] leading to a higher risk of fibrosis progression, early cirrhosis, and hepatocellular carcinoma.[3]

The prevalence of HCV infection in pediatric patients with lymphoproliferative diseases has most commonly been reported with B cell Non-Hodgkin lymphoma.[4] There is limited data on HCV in children with acute lymphoblastic leukemia (ALL). For pediatric ALL survivors treated before 1990, HCV RNA positivity has been reported in 6.6%–49% of cases.[5] A study conducted in Chile in 2001 identified 4 out of 34 pediatric ALL cases to have detectable HCV RNA levels, attributed to immunosuppression and blood transfusions.[6] In India, Arora *et al*., in 2003, reported detectable HCV RNA in 38% of pediatric cancer patients.[7] Case studies have reported the requirement of dose reduction or suspension of chemotherapy in 80% of pediatric ALL cases who are anti-HCV positive owing to hepatotoxicity.[8]

The standard of care anti HCV therapy in children aged 3–17 years had been peginterferon and ribavirin for 48 weeks.[9] Given the suboptimal efficacy and substantial toxicity of this therapy, new all-oral interferon-free direct-acting antiviral regimens gained acceptance for clinical trials in children after their successful performance in the adult population. With their implementation and clinical use, the WHO, has set the goal of eliminating hepatitis C as a public health threat by 2030.[1] To attain this goal, a recently published descriptive review has highlighted the role of further studies after the recent Food and Drug Administration (FDA) approval of pan-genotypic, anti-HCV regimen, sofosbuvir/velpatasvir (SOF/VEL), for the pediatric population >6 years of age or >17 kg body weight in March 2020.[10,11] We herein report a case of an HCV-infected

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pediatric B cell ALL patient who was treated with SOF/VEL concomitantly with an intensive chemotherapy regimen. To the best of our knowledge, in pediatrics, this is the first report of SOL/VEL use after its FDA approval.

Case Report

A 9-year-old boy was referred to our hospital with complaints of easy fatigability and low-grade fever for 4 months, multiple petechiae spots over the body for 15 days, and hematuria with melena for 4 days. He had received multiple blood transfusions for anemia. On examination, the child had pallor, multiple petechiae over the face and trunk, nontender right anterior cervical and bilateral inguinal lymphadenopathy with massive hepatosplenomegaly (firm/nontender/smooth surface with lower edge palpable 7 cm and 9 cm below costal margin respectively). No icterus or pedal edema was noted. Rest systemic examination was within normal limits. Immunophenotyping studies were consistent with B-cell ALL. Pre-chemotherapy workup revealed tests negative for the hepatitis B virus and human immunodeficiency virus. Serologic evaluation for the HCV antibody done by chemiluminescent microparticle assay was positive, with a significant ratio of 10.11 S/CO units. Treatment options for anti-HCV therapy were discussed with the family and four-drug (steroid, anthracycline, l asparagine, and vincristine) high-risk chemotherapy initiated awaiting HCV RNA copies.

Subsequent to the initiation of the induction regimen, there was a persistent elevation of alanine transaminases >3 × upper limit of normal (ULN) (ranging from 224 to 503 U/L; ULN = 40 U/L) with no signs of hepatic decompensation (jaundice/ascites/encephalopathy or coagulopathy). Laboratory parameters are as shown in Table 1. HCV RNA polymerase chain reaction assay detected baseline hepatitis C virus RNA 4,814,219 IU/ml, with log value 6.68 (detection limit 50 IU/ml 1.7 log). Ultrasound abdomen revealed hepatosplenomegaly (Liver 15.6 cm, Spleen 14 cm) with normal hepatic echotexture and no evidence of ascites. With worsening liver enzymes and high viral load, it was decided to treat the child for HCV.

SOF (200 mg) plus VEL (50 mg) was started once a day for 12 weeks. We continued chemotherapy as per protocol with regular liver function test monitoring. The end induction bone marrow was in morphological remission and was continued on the high-risk consolidation phase. At the end of 4 weeks of antiviral therapy, liver enzymes returned to normal, and serum HCV RNA was undetectable. He was planned for 12 weeks of DAA and HCV genotype was confirmed to be Type 3. The child had a transient increase in liver enzyme attributed to ongoing chemotherapy. HCV RNA was undetectable at 12 weeks of starting oral DAA.

Discussion

Our patient had persistent transaminitis, positive anti-HCV antibody, and HCV RNA with no clinical signs of underlying cirrhosis. Thus, he was diagnosed with an active current HCV infection.

The HCV guidance panel of the 2019 American Association for the study of Liver Diseases and Infectious Diseases Society of America recommends DAA treatment for all children (age 3yrs or more) and adolescents with HCV infection.[12] The appropriate drug combination is selected based on host and viral factors: Age, treatment status, evidence of cirrhosis, and HCV genotype. Ledipasvir/sofosbuvir and sofosbuvir/ribavirin are approved for those aged 3 years or more in HCV genotypes 1,4,5,6 and genotypes 2/3, respectively. SOF/VEL is also an option for children aged 6 to <18 years with HCV infection.[10] This combination was noted to have sustained virological response-12 rates of >92% across all genotypes with a good safety profile.

With recent approval for use in pediatric population, safety, and efficacy data among immunosuppressed subgroups is limited. The use of oral DAA therapy in these subgroups has been confined to cancer survivors after completion of chemotherapy[13] or in those after completion of hematopoietic stem cell transplant.[14] A solitary report has outlined the use of sofosbuvir/ledipasvir in a 4-year-old child with HCV genotype 1b during maintenance therapy for ALL.[15]

Concerns for concomitant antiviral and chemotherapy stem from the evidence of HCV reactivation and hepatic flares due to immunosuppression by chemotherapy,[16] potential drug interactions, and overlap between toxic effects of anti HCV therapy with cytotoxic chemotherapy. The use of anti-HCV therapy and the subsequent elimination of the virus confers

Table 1: Lab parameters prior to and post-initiation of anti-hepatitis C virus therapy (using sofosbuvir and velpatasvir) in a child undergoing induction chemotherapy

Parameter	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 12
ALT (U/L)	224	503	365	220	68	32	80
AST (U/L)	158	181	116	112	50	40	64
Total bilirubin (mg/dl)	1.9	2.2	1.5	1.5	1.2	0.8	0.8
PT/INR	13.8/1.1	-	-	12.6/0.9	-	-	-
Serum albumin (mg/dl)	3.0			3.4			3.8
HCV RNA copies (IU/ml)		>4.8 million				None detected	None detected

ALT: Alanine transaminases, AST: Aspartate aminotransferase, PT: Prothrombin time, INR: International normalized ratio, HCV: Hepatitis C virus

infected cancer patients with virologic, hepatic, and oncologic advantages.[12,17,18] Thus, overall survival rates are improved with lower morbidity.

Our patient showed an undetectable level of HCV RNA at 4 and 12 weeks of therapy with oral sofosbuvir and velpatasvir. This combination decreases viral replication by inhibiting NS5b RNA dependent RNA polymerase and NS5a protein, respectively. Except for a brief period of febrile neutropenia well managed with antimicrobials, no other severe gastrointestinal, psychiatric or hematologic toxicity was noted in the patient. He had no clinical or laboratory evidence of hepatic flares (except those attributed to chemotherapy) or hepatic decompensation. Concomitant chemotherapy was well tolerated with no interruptions or dosage adjustments.

In conclusion, we report that sofosbuvir with velpatasvir was well tolerated concomitantly with intensive chemotherapy in an HCV infected pediatric ALL case, and on follow-up had sustained virologic response. Oral DAAs are an effective therapy not only for controlling HCV replication and for decreasing viral load in cancer patients but also help in improving their overall survival rates with the added hepatic and oncologic benefits. This is the first report of successful treatment after the recent FDA approval of sofosbuvir and velpatasvir in pediatrics. This holds significance for future use of newly approved DAAs in the pediatric population to meet the WHO 2030 goal.

Limitations

The use of SOF-VEL with chemotherapy requires study on a larger group to understand the various drug interaction and tolerability and the virological response needs to be followed over a longer duration.

Declaration of patient consent

The authors certify that they have obtained patient consent before submitting the case report. As part of the consent process, the legal guardian has given his consent for the clinical information reported herein to be published. It has been explained that due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Research quality and ethics statement

The authors followed applicable EQUATOR Network ("http://www.equator-network.org/) guidelines, notably the CARE guideline, during the conduct of this report

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Nil.

Conflicts of interest

There are no conflicts of interest.

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