Hepatic veno-occlusive disease (VOD), also called sinusoidal obstruction syndrome, is rapidly progressing and involves life-threatening complications that can occur in patients receiving chemotherapy and/or bone marrow transplantation. No completely satisfactory treatment strategies have yet been established. We present a case of rhabdomyosarcoma in a 21-month-old boy who developed pancytopenia, dyspnea, jaundice, massive ascites and body weight gain of more than 10% after receiving conventional chemotherapy. Hepatic VOD was diagnosed. He recovered after supportive care and treatment with high-dose methylprednisolone.

1. Introduction

Hepatic veno-occlusive disease (VOD) is a well-known complication of conditioning regimens used for stem-cell transplantation.1-3 Its incidence varies from less than 5% to as high as 70% in different reports.2 The pathogenesis of VOD was once considered to be due to obstruction of hepatic venules and small sublobular veins by microthromboses.4 Recent studies have suggested that the primary toxic injury to sinusoidal endothelial cells, followed by a series of biologic processes, leads to circulatory compromise of the centrilobular hepatocytes, fibrosis, and obstruction of liver blood flow.5 Thus, sinusoidal obstruction syndrome seems a more appropriate term.

Recently, VOD has been increasingly recognized as a complication of conventional chemotherapy, with or without abdominal irradiation, especially in patients with Wilms’ tumor treated with dactinomycin.6 There are currently no satisfactory treatments available. We present our experience with a young boy with hepatic VOD who was treated successfully with high-dose methylprednisolone (HDMT).

2. Case Report

A 21-month-old male patient initially presented with a left submandibular mass with extension to the ipsilateral periauricular area. Yellowish discharge and...
bleeding were noted in the left ear canal. He was brought to a local hospital, where head and neck computed tomography revealed a 5 × 4-cm mass with central hypodensity and encroachment of the left facial nerve. He was transferred to our hospital, and rhabdomyosarcoma, Intergroup Rhabdomyosarcoma Study Group III, was diagnosed by histologic examination. Chemotherapy, consisting of vincristine 1.5 mg/m²/day on Day 1, dactinomycin 0.5 mg/m²/day on Days 1-5, and cyclophosphamide 2.2 g/m²/day on Day 1 (i.e., the VAC regimen) and alternating with vincristine 1.5 mg/m²/day on Day 1, etoposide 100 mg/m²/day on Days 1-5, and 1.8 g/m²/day ifosfamide on Days 1-5 (i.e., the VEI regimen), was administered every 3 weeks. The first courses of VAC and VEI chemotherapy were uneventful, except for the development of pancytopenia and neutropenic fever.

The patient developed fever and abdominal distention on the third day (Day +8 from the start of chemotherapy) after completing the second course of the VAC regimen. A complete blood count revealed pancytopenia (white blood cells [WBC], 500/mm³; hemoglobin [Hb], 9.6 g/dL; platelets, <3000/mm³). C-reactive protein (CRP) was 2.8 mg/dL. A chest X-ray showed right-sided pleural effusion. Empiric antibiotics were prescribed after septic workup. The patient’s condition worsened rapidly because of dyspnea. His body weight had increased by more than 10% (from 12.9 to 15 kg). Laboratory tests showed WBC <200/mm³, Hb of 6.9 g/dL, platelet count of 1000/mm³, aspartate aminotransferase (AST) of 118 U/L, alanine aminotransferase (ALT) of 54 U/L, total bilirubin of 1.1 g/dL, direct bilirubin of 0.51 g/dL, blood urea nitrogen (BUN) <1 mg/dL, creatinine (Cr) of 0.2 mg/dL, Na of 136 mmol/L, K of 3.6 mmol/L, Cl of 102 mmol/L, and albumin of 3 g/dL. Activated partial thromboplastin time was normal, prothrombin time was prolonged further (16.5 seconds; INR = 1.56). BUN was 3 mg/dL and Cr 0.4 mg/dL. On the morning of Day +14, serum AST, ALT, total bilirubin, BUN, and Cr were 1108 U/L, 489 U/L, 2.9 g/dL, 5 mg/dL, and 0.5 mg/dL, respectively, and by Day +15, serum AST, ALT, total bilirubin and direct bilirubin had risen to 1494 U/L, 781 U/L, 3.4 g/dL, and 1.51 g/dL, respectively. Thereafter, the patient’s condition improved gradually. One week later (Day +20), serum AST, ALT and total bilirubin had returned to 91 U/L, 197 U/L, and 1.4 g/dL, respectively. Blood and urine cultures were sterile. The highest CRP level during this period was 32.7 mg/dL. Work-ups for hepatitis A, B, C, and cytomegalovirus were all negative. Neither side effects due to HDMT nor sequelae of VOD were noted. After the patient’s general condition had improved and the laboratory data returned to normal, the VAC regimen was replaced by the VEC regimen (vincristine 2 mg/m²/day on Day 1, epirubicin 30 mg/m²/day on Days 1-2, and cyclophosphamide 10 mg/m²/day on Days 1-3) because of refusal of further VAC treatment by the patient’s family. Follow-up liver function tests were within normal limits, and abdominal echography was negative for abnormal findings up to the completion of a 1-year course of chemotherapy.

3. Discussion

The gold standard for the diagnosis of VOD is based on histological examination of liver tissue. However, this is often not feasible due to coexisting refractory thrombocytopenia and coagulopathy.²⁴⁷ Clinical criteria for the diagnosis of VOD have been drafted by Seattle and Baltimore groups.⁸⁹ According to the Seattle criteria, two of the three signs (jaundice, painful hepatomegaly and fluid retention) must be present. The Baltimore criteria include jaundice (total bilirubin >2 mg/dL) plus at least two of the following signs: hepatomegaly (usually painful), ascites and >5% weight gain. Our case fulfilled the criteria of both groups. However, the diagnosis of VOD must be carefully differentiated from those of sepsis, viral hepatitis, fungal infection, drug-related cholestasis and hepatotoxicity, and tumor infiltration.

The severity of VOD is defined retrospectively following clinical observations. Mild VOD resolves without intervention; moderate VOD requires medical treatment but is resolved completely; severe VOD progresses to multiorgan failure or causes death.¹³ Multiorgan failure is defined as either oxygen requirement with an oxygen saturation of 90%
or less on room air and/or ventilator dependence; and/or renal dysfunction (defined as a doubling of baseline creatinine and/or dialysis dependence); and/or encephalopathy, in addition to liver failure. However, this model can only provide a retrospective assessment of severity.

Many groups have reported an increased risk of VOD after bone marrow transplantation, but information about the effects of conventional chemotherapy is still scarce. Arndt et al cited age as the greatest risk factor for the development of hepatopathy after VAC therapy. In their study, the risk of hepatopathy was 4% in children 3 years of age or older, and climbed to 15% in patients under 3 years of age. Furthermore, in the children under 3 years old, only one patient was less than 1 year old; all others were between 1 and 3 years of age. The chemotherapy dose used in the patients younger than 1 year was 50% of that used in the older children. In contrast, the dosage used in 1–3-year-olds was relatively high. Dose modification in this age group should be considered in order to decrease the incidence of VOD. Furthermore, an uneventful course of VAC therapy does not guarantee the absence of VOD in subsequent courses: two-thirds of VOD occurred during the second or third courses of VAC therapy. In our 21-month-old patient, VOD developed during the second cycle, consistent with the increase of its administration deserve further investigation.

Efficient therapy for VOD is not yet well established. Supportive treatment with blood component replacement is vital. Anticoagulation therapy, such as tissue-plasminogen activator with or without concurrent heparin, might be beneficial, but is associated with significant risk of life-threatening bleeding. Prostaglandin E1, glutamine, and vitamin E have been used, albeit in mostly anecdotal reports and in small case series. Defibrotide has been reported to show promise in the treatment of VOD, and complete resolution of VOD was seen in 36% of patients, with 35% survival at Day +100. No severe hemorrhage or serious toxicities were reported, but defibrotide is not universally available.

Corticosteroids, which are potent inhibitors of cytokine production, have been used as prophylaxis for graft-versus-host disease for a long time. Khoury et al used HDMT to treat regimen-related hepatic toxicity after bone marrow transplantation and observed a 61% response rate. In their study, however, some patients were treated early, after the development of hyperbilirubinemia, and in the absence of other criteria of VOD. Moreover, earlier use of corticosteroids may increase the risk of superimposed infections. Akyüz et al also used HDMT to treat hepatic VOD arising after conventional chemotherapy in a child with Wilms' tumor who had previously received abdominal irradiation. HDMT was given to our patient because of impending respiratory failure after intensive supportive care. AST, ALT, and bilirubin levels increased initially and gradually declined 3 days later, implying a response to HDMT. No apparent complications, such as hyperglycemia, hypertension, or bleeding, were observed during the remaining treatment course. However, our patient’s recovery could be attributed partly, if not entirely, to spontaneous improvement following meticulous supportive care. In a large series report, 10 of 821 patients with rhabdomyosarcoma developed VOD after receiving conventional chemotherapy. One of the 10 patients died and one developed portal hypertension. Five of the remaining eight patients were switched to other regimens, while the other three patients continued to receive the same regimen but at 25% of the initial administrated dose. The dose was slowly escalated to the full dose if the patients showed no signs of hepatotoxicity. None of these eight patients developed recurrent VOD. The importance of good supportive care and avoidance of aggressive diuresis cannot be overemphasized. Randomized controlled trials are required to determine the efficacy of HDMT.

In summary, we have reported our experience of using HDMT to treat hepatic VOD in a child with rhabdomyosarcoma who was receiving conventional chemotherapy. The efficacy of HDMT and the timing of its administration deserve further investigation.

References


