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Veno-occlusive disease with multi-organ involvement following actinomycin-D

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Abstract

Actinomycin-D (Act-D) is a rare cause of veno-occlusive disease (VOD). Between 1993 and 1998, we managed 6 patients, all male, median age 19 months (range 6–48 months) who received Act-D for Wilms' tumour ($n=4$), clear cell sarcoma ($n=1$) or rhabdomyosarcoma ($n=1$). VOD presented with a median platelet count of 12×10^9/l, INR 3.8, fibrinogen 16 mg/l, fibrinogen degradation products (FDPs) $\geqslant$80 μg/l, aspartate aminotransferase (AST) 6922 IU/l, bilirubin 47 μmol/l. In 3 cases, transient liver dysfunction and thrombocytopenia without neutropenia had been observed after a previous course of Act-D. All six children developed encephalopathy, hepatomegaly, ascites, reversed portal flow and renal impairment. All received mechanical ventilation and two required haemofiltration. The treatment was supportive. Severe Adult Respiratory Distress Syndrome developed in 3 patients, all of whom died. 3 patients recovered. The outcome of VOD with multi-organ failure is poor. Intravascular coagulopathy precedes and characterises severe VOD during Act-D treatment.

Keywords: Veno-occlusive disease; Multi-organ failure; Children; Actinomycin-D; Wilms' tumour

1. Introduction

Veno-occlusive disease (VOD) was first described 50 years ago in Jamaican children as 'Jamaican bush tea disease' because all those affected had ingested teas made from local plants. Epidemiological studies revealed that the children first developed 'hepatitis' followed by onset of right upper quadrant pain, liver enlargement and ascites. Liver biopsy showed non-thrombotic hepatic venule occlusion by intimal proliferation and fibrosis, accompanied by centrilobular necrosis sparing the portal areas (Fig. 1) [1].

These days, VOD is more likely to be encountered after non-surgical cancer treatment, especially chemotherapy and radiotherapy, either after combinations of myeloablative drugs and radiotherapy (so-called 'conditioning') before bone marrow transplantation (BMT) [2–8], or after standard dose chemotherapy including Actinomycin-D (Act-D) [9–24]. Children treated for Wilms' tumour seem to be particularly susceptible to VOD. The most serious and life-threatening complication of VOD following Act-D is multi-organ failure, which to date has only been reported in 3 patients [9,16]. Such complication is particularly tragic during the treatment of highly curable tumours such as Wilms'.

In an attempt to identify possible predisposing factors and predictors of outcome, we have reviewed the clinical and laboratory features of 6 consecutive children referred to our Unit over a period of 5 years for the management of VOD after Act-D treatment and who developed multi-organ involvement.

2. Patients and methods

The medical records of the six consecutive children referred to our Supra-Regional Paediatric Liver Service between 1993 and 1998 for the management of VOD and multi-organ dysfunction after Act-D treatment were reviewed retrospectively.

VOD was diagnosed on the basis of McDonald's criteria and specifically in the presence of at least two of the following: (a) jaundice (serum bilirubin >27 μmol/l);

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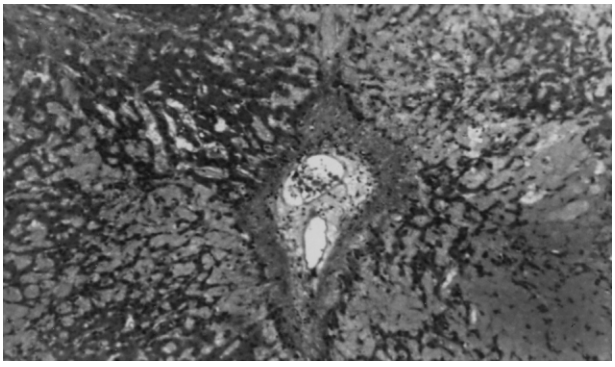

Fig. 1. Histology of veno-occlusive disease. The centrilobular vein is occluded by debris, zone 3 is necrotic and surrounded by severely congested sinusoids.

(b) tender hepatomegaly; (c) ascites or excessive weight gain [25]. The clinical onset was considered to be the time at which the McDonald's criteria were satisfied. Multi-organ involvement was defined as the association of impaired function of the liver plus one or more other organ systems. The respiratory system was considered involved when mechanical ventilation and increased oxygen requirement were needed. The oxygen requirement was measured by the oxygenation index (OI) (fraction inspired of oxygen×mean airway pressure/PaO2), where mean airway pressure = ((peak inspiratory pressure×inspiratory time) + (positive end expiration pressure×(60/respiratory rate)−inspiratory time)/60/respiratory rate). The ventilation requirement was measured by the ventilation index ($VI = pCO_2 \times$ respiratory rate×peak inspiratory pressure/1000). The kidneys were considered involved when creatinine was at least double the pre-VOD values and oligo (urine output <1 ml/kg/h)-anuria was present. Intravascular coagulopathy was defined as an international normalised prothrombin ratio (INR) greater than 1.2 in the presence of thrombocytopenia and an increased concentration of circulating fibrin degradation products. Isolated thrombocytopenia (IT) was defined as a platelet count of $<50\times10^9$/l with a neutrophil count greater than 1.0×10^9/l.

3. Results

All 6 patients were male (median age at presentation 19 months, range 6–48 months), four had Wilms' tumours, one had a clear cell sarcoma of the left kidney and one had a paratesticular rhabdomyosarcoma; all had been given a good probability of cure. All four Wilms' tumours were right-sided and 5 patients had had their tumour removed before the onset of VOD (Table 1).

3.1. Chemotherapy

4 patients (patients 1, 2, 4 and 5) were treated with Act-D (1.5 mg/m^2 3 weekly) and vincristine (1.5 mg/m^2 weekly) for stages 1–3 Wilms' tumour (protocol UKW3 Wilms' 9101), but 1 of them (patient 4) was changed to regimen 6 of the same protocol, containing doxorubicin (30 mg/m^2 3 weekly), 6 months after presentation because of tumour recurrence in the lungs. One child (patient 3) with a clear cell sarcoma of the left kidney had been treated with Act-D (1.5 mg/m^2 3 weekly), vincristine (1.5 mg/m^2 weekly) and doxorubicin (30 mg/m^2 3 weekly) according to the UKW3 Wilms' 9101

Table 1
Oncological history and haematological parameters

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age at onset[a]	4 years	6 months	21 months	15 months	18 months	32 months
Sex	Male	Male	Male	Male	Male	male
Diagnosis	Wilms' tumour	Wilms' tumour	CC sarc	Wilms' tumour	Wilms' tumour	Rhabdo
Site	Right kidney	Right kidney	Left kidney	Right kidney	Right kidney	Testis
Stage	2	3	3	1	3	1
Chemotherapy	Vincristine Act-D	Vincristine Act-D	Vincristine Act-D doxorubicin	Vincristine Act-D doxorubicin	Vincristine Act-D	Vincristine Act-D
Tumour excision before VOD	Yes	Yes	Yes	Yes	No	Yes
IT recorded after most recent Act-D	8 days	5 days	5 days	6 days	10 days	7 days
Platelet count at onset[a] (NV: 150–450 $\times10^6$/l)	23	4	11	13	48[b]	12
Fibrinogen at onset[a] (NV: 2–4.5 mg/l)	19	1	140	320	21	11
FDP at onset[a] (NV: <0.4 μg/l)	80–160	80–160	>160	80–160	NA	>160
Anti-platelet Ab	Absent	Absent	NA	NA	NA	Absent

IT, isolated thrombocytopenia; CC sarc, clear cell sarcoma of kidney; Rhabdo, rhabdomyosarcoma; Act-D, actinomycin-D; FDP, fibrin degradation products (D-Dimer); Ab, antibodies; NA, not available.

[a] Onset is considered the time when McDonald's criteria were satisfied.

[b] After platelet transfusion.

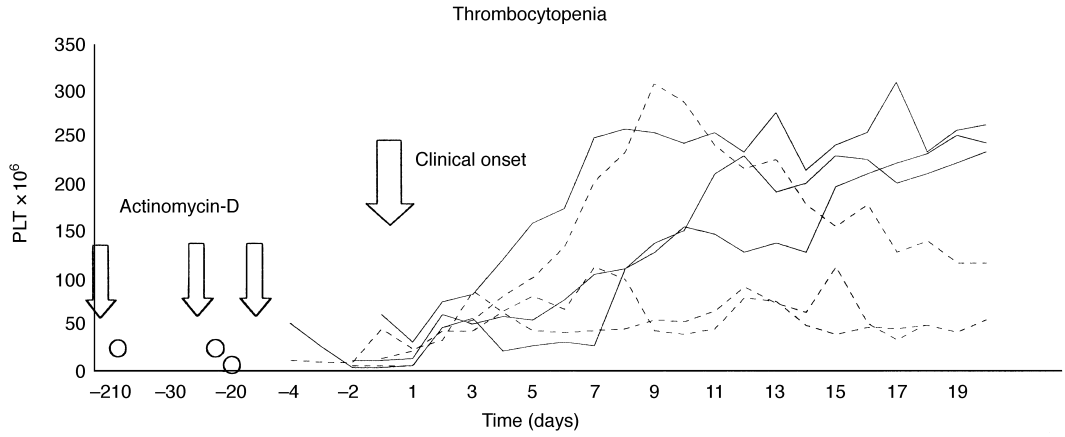

Fig. 2. Clinical course of thrombocytopenia. The dashed line indicates those cases with fatal outcome (patients 1, 3 and 4). The circles indicate the nadir of isolated thrombocytopenia after the preceding dose of actinomycin-D (patients 1, 4 and 6). All 3 patients received actinomycin-D doses in correspondence to the small arrows. Plt, platelet count.

protocol, regimen 5. The sixth patient (patient 6) was treated with Act-D and vincristine according to the protocol MMT89 for rhabdomyosarcoma stage 1. All six children presented with severe VOD 7 to 10 days after the second (5/6) or third (1/6) consecutive Act-D-containing course of treatment. None had had radiotherapy (Table 1).

3.2. Haemostasis

Thrombocytopenia without neutropenia was one of the earliest signs and was evident before the clinical onset of VOD in all four children for whom serial platelet counts were available. In all 6 patients, the disease presented with intravascular coagulopathy with a median platelet count of 12×10^9/l (range 4–48×10^9/l), median INR of 3.8 (range 2.2–5.5), median fibrinogen 1.6 mg/dl (range 10–32 mg/l, normal values 20–45 mg/l); fibrin degradation products (FDPs) (normal values <40 μg/l) were $\geqslant80$ μg/l in 5/5 patients tested. In three cases (patients 1, 3 and 4), for whom previous laboratory results were available, isolated thrombocytopenia was also seen after the preceding course of Act-D. Antiplatelet antibodies, tested in 3 patients, were negative (Table 1). In the 3 patients who eventually died, elevated FDPs and thrombocytopenia characterised the course persisting until death in 2 (patients 1 and 3) and fluctuating until death in 1 (patient 4). In those patients who survived (patients 2, 5 and 6), thrombocytopenia disappeared by 7 days after the onset of VOD (Fig. 2).

3.3. Liver

At diagnosis of VOD the median aspartate aminotransferase (AST) was 6922 IU/l (range 4140–16 328 IU/l, normal value <50 IU/l), median γGT 46 IU/l (range 33–81 IU/l, normal value <50) and median bilirubin 47 μmol/l (range 28–75 μmol/l, normal value <20). During the course of the disease, the bilirubin peaked at a median of 225 μmol/l (range 76–1250 μmol/l) at a median of 16 days after the last Act-D dose. AST levels reached a median peak of 15 087 IU/l (range 10 995–20 490 IU/l) at a median of 9 days after the last Act-D dose, and decreased rapidly within 4–6 days irrespective of the outcome (Table 2, Fig. 3a and b). Encephalopathy with hepatomegaly and ascites were present at clinical onset and all 6 patients had reversed portal flow demonstrated by ultrasound (6 patients) and angiography (1 patient) with increased arterial flow and patent hepatic veins and vena cava. Forward flow returned in all patients, including those with ongoing multi-organ failure, after a median of 10 days (range 4–20 days) from the onset.

3.4. Kidneys

All 6 patients had renal impairment with increased plasma creatinine (median 92, range 72–271 μmol/l) and urea (median 15.6, range 8.4–26.5 mmol/l) levels compared with their basal values (median creatinine 38, range 35–53 μmol/l; median urea 4.4, range 2.7–6.8 mmol/l), consistently peaking about 1 week after the clinical onset (Table 2, Fig. 3c). 2 patients required haemofiltration because of anuria. The Doppler scan of the renal arteries demonstrated high vascular resistance in 2 of 3 patients tested.

3.5. Lungs

Mechanical ventilation was initiated in the local hospital in 2 patients, and in our unit in 4 patients on admission. All required oxygen supplements. Lung failure with the characteristics of adult respiratory distress syndrome (ARDS) developed in 3 patients (patients 1, 3 and 4). Maximum oxygenation index was a median of 21.5 (range 2–46) and maximum ventilation index was a

Table 2
Details of hepatic and renal dysfunction after clinical onset[a]

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Onset after last Act-D	8 days	7 days	8 days	10 days	10 days	8 days
AST at onset (IU/l)	4725	11 300	4140	4674	16 328	9120
Max AST (IU/l)	13 810	11 300	20 490	10 995	16 328	17 600
GGT at onset (IU/l)	45	81	79	33	47	35
Bilirubin at onset (μmol/l)	28	75	67	29	41	54
Max bilirubin (μmol/l)	1250	217	236	233	76	137
INR at onset	5.5	5	2.2	3.2	4.2	3.5
Max INR	5.5	5	3.5	5.2	4.2	3.5
Encephalopathy	Yes	Yes	Yes	Yes	Yes	Yes
Creatinine pre-VOD (μmol/l)	53	36	37	40	35	44
Max creatinine (μmol/l)	271	74	204	93	72	90
Urea pre-VOD (mmol/l)	2.7	4.3	3.8	3.8	5.2	6.8
Max urea (mmol/l)	26.5	11	21.8	13.8	8.4	17.4
Haemofiltration lasted	20 days	–	6 days	–	–	–

Act-D, actinomycin-D; Max, maximum; GGT, gamma glutamyl transpeptidase; AST, aspartate aminotransferase; INR, international normalised ratio; A dash (–) indicates that the information is not applicable.

[a] Onset is considered the time when Mc Donald's criteria were satisfied.

median of 49.5 (13–139). The 3 patients who survived (patients 2, 5 and 6) required mechanical ventilation for 2, 5 and 9 days, while the 3 who died were ventilated for 16, 21 and 24 days. Among these 3 patients, 2 (patients 1 and 3) died as a consequence of respiratory failure and pulmonary haemorrhage, while 1 died of tumour recurrence (Table 3, Fig. 3d).

3.6. Treatment and outcome

The supportive treatment described in Table 4 was given to all patients. Recombinant tissue plasminogen activator (rTPA) (Alteplase, Actilyse® Boehringer Ingelheim, Germany, 2 mg intravenous (i.v.) bolus and 8 mg 12-h infusion) followed by heparin (150 U/kg subcutaneously (s.c.) every 12 h) was administered to patient 6 in an attempt to reverse the veno-occlusive process. The patient recovered, although he experienced severe bleeding from the central line insertion. Nitric oxide (NO) was administered to patients 1 and 4 in an attempt to improve oxygenation, with transient reduction of oxygen dependence, but no sustained benefit (Fig. 3d). Prostacyclin (Epoprostenol, Flolan® Glaxo-Wellcome, UK) was used in patient 1 to improve lung

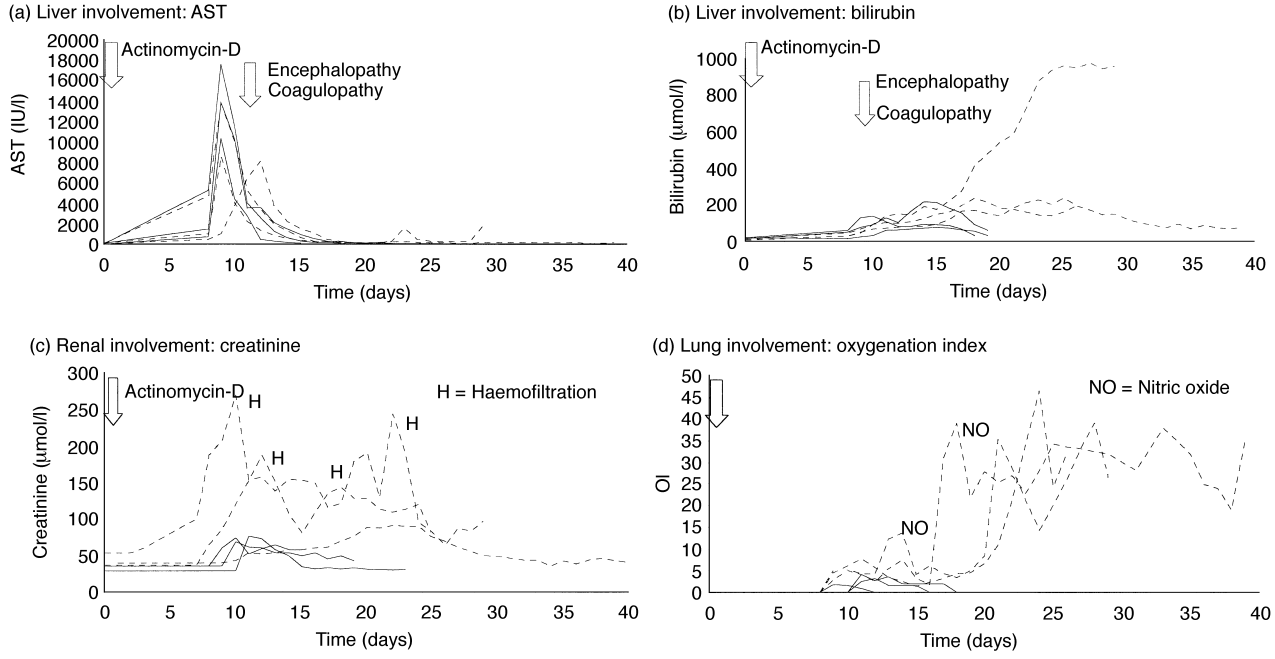

Fig. 3. Clinical course of liver, renal and lung involvement. The dashed line indicates those cases with fatal outcome (patients 1, 3 and 4). Crea, creatinine.

Table 3
Details of lung dysfunction and outcome

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Max oxygenation index	39	2	46	39	3.2	4.1
Max ventilation index	139	16	125	63	36	13
Ventilation lasted	21 days	2 days	16 days	24 days	5 days	9 days
Days in PICU	22 days	8 days	18 days	29 days	9 days	18 days
Outcome	Dead	Alive	Dead	Dead	Alive	Alive
Follow-up (months)	–	34	–	15	20	56
Cause of death	MO failure[a]	–	MO failure[a]	Tumour relapse	–	–

PICU, Paediatric Intensive Care Unit; MO, multi-organ; Max, maximum; A dash (–) indicates that the information is not applicable.
[a] bleeding, hypoxia, cardiovascular collapse. See text for oxygenation index and ventilation index.

perfusion with no appreciable clinical effect. 3 patients died, 2 from complications of multi-organ failure (bleeding, hypoxia, cardiovascular collapse) at days 22 and 18 (patients 1 and 3), and 1 from recurrence of Wilms' tumour 15 months after VOD (patient 4). In this case, a prolonged and severe course of VOD had delayed the resumption of anti-tumour treatment. 2 patients (patients 2 and 6) were not treated with any further chemotherapy after recovering from VOD; patient 5 received two more courses of vincristine; these 3 patients are alive, well and tumour-free after a median follow-up of 34 months (Table 3).

4. Discussion

The treatment of childhood cancer has improved dramatically over the last 30 years. The cure rate for children with Wilms' tumour is now over 80% and for good prognosis rhabdomyosarcoma between 60 and 70%, but in both conditions treatment-induced VOD can adversely affect the outcome. Although this complication has been recognised for many years, the poor understanding of its underlying pathophysiology has prevented effective treatment.

VOD is well recognised after BMT, its incidence being described as high as 28% in paediatric series [2]. Associated multi-organ failure is also not uncommon in this setting, with some series reporting an incidence of renal impairment of 54% [7] and mortality as high as 41% [8]. However, BMT may be followed by several complications, making it difficult to discriminate whether patients die from VOD or with VOD.

Table 4
Supportive treatment in the management of veno-occlusive disease in children

Fluids and sodium restriction
Preservation of good intravascular volume with blood and fresh frozen plasma
Preservation of good oncotic pressure with human albumin aiming for levels > 30 g/l
Maintenance of platelets $>30\times10^9$/l, Hb >80 g/l, INR <2.5
Broad spectrum antibiotics and antifungals
N-acetylcysteine 100 mg/kg in 48 mls of 5% dextrose: 2 ml/h standard infusion until INR < 1.3
Vitamin K 0.2 mg/kg daily until INR < 1.3
Spironolactone up to 6–8 mg/kg/day in 2 doses
Octreotide 500 mcg diluted in 40 ml of 0.9% saline: 2 ml/h standard infusion irrespective of body weight

Whilst alarming clinically, VOD after Act-D is usually a non life-threatening condition, characterised by a slight to moderate derangement of liver function, right upper quadrant tenderness or hepatomegaly and weight gain, all usually reversible with conservative treatment (Table 4). With increased awareness of VOD among paediatric oncologists, the reported incidence in recent publications [20] has been as high as 8% of all children treated for Wilms' tumour (Table 5). Of 41 children with Wilms' tumour who developed VOD reported by Bisogno and colleagues [20], 47% had liver enzymes greater than 10 times the upper normal values, but none developed renal or lung failure and none died. However, anecdotal cases of VOD leading to multi-organ failure following Act-D treatment for Wilms' tumour have been published. Thus, Green and colleagues reported a patient who died from renal failure and another who required assisted ventilation [9], while Culic and coworkers reported a child who developed respiratory failure and died 6 days after the onset of VOD [16]. Our series of 6 patients with VOD-associated multi-organ failure after Act-D is the largest series to date and some of our observations may allow a better understanding of the pathogenesis of this condition. Not being an oncology centre, we are not in the position of establishing how many cases of VOD following Act-D treatment do progress to the same degree of multi-organ failure, which prompted the referral of the six children to our tertiary Paediatric Hepatology Service. Interestingly, all our patients were boys, but only a larger prospective study will be able to show whether the male sex predisposes to more severe VOD.

The most striking feature in all our patients was the presence of isolated thrombocytopenia with fibrinolysis before the onset of the disease (Fig. 2). Although Raine and colleagues have observed thrombocytopenia concomitantly with VOD in 6 patients treated with Act-D,

Table 5
Prevalence of VOD and mortality in children treated for solid tumours

Group [Ref.]	No. of patients	Criteria	Act-D dosage per course (mg/m^2)	Incidence of VOD *n* (%)	Incidence of fatal VOD *n* (%)
UKW1 [21]	501	Jones + low Plt	1.5	6 (1.2)	0
NWTS [9,10][a]	319	Other	1.5–1.8	14 (4.4)	1 (7)
SIOP9/GPOH [20]	511	McDonalds	1.5	41 (8)	0
Brazilian Group [12]	65	Other	1.5	1 (1.5)	0
IRS4 [14]	821	McDonalds	1.5	10 (1.2)	1 (10)

UKW, United Kingdom Wilms' Tumour; NWTS, National Wilms' Tumour Study; SIOP, International Society of Pediatric Oncology; GPOH, German Paediatric Oncology and Haematology Group; IRS, Intergroup Rhabdomyosarcoma Study; Plt, platelets count.

[a] Includes two groups of patients treated with single actinomycin-D (Act-D) dose (1.5 or 1.8 mg/m^2) and one group treated with divided doses (1.5 mg/m^2).

and suggested to call the disease 'Hepatopathy-Thrombocytopenia syndrome', they did not report data on fibrinolysis [21]. Akin to our findings, thrombocytopenia and fibrinolysis were reported in the two cases described by Adachi and Matsuda [15] and by Culic and colleagues [15,16]. This observation suggests that intravascular coagulopathy is likely to play an important role in the pathogenesis of VOD. A sustained reduction of circulating platelets, probably as a result of persistent DIC, seems also to correlate with a poor prognosis, as seen in our patients who died. Although in our group only 1 patient received treatment with rTPA, our finding of early DIC would suggest that this treatment should be beneficial. However, the possible benefit should be weighed against the increased risk of bleeding. Previous studies, mainly carried out in bone marrow transplant recipients, have demonstrated abnormalities in cytokine and clotting factor profiles before and during VOD, supporting the hypothesis that abnormal haemostasis is the initiator of this hepatic complication [26–33]. Whether DIC may be implicated also in the causation of kidney and lung damage of patients who develop multi-organ failure is speculative. In our series, endothelial involvement of the renal and lung vessels is indirectly suggested by the high resistance in the renal arteries demonstrated by Doppler ultrasound in 2 of our patients and by the temporary reduction in oxygen requirement after nitric oxide administration in two further children. Several drugs have been used with the aim of counteracting the coagulopathy, rTPA being the most successful, even if controversial because of its effect of increasing the bleeding tendency [34–41].

It is of interest and of clinical importance that isolated thrombocytopenia, was present after previous Act-D courses without leading to a fully expressed VOD in the 4 patients for whom records were available. This confirms the view of Raine and colleagues [21] that thrombocytopenia could be used as a sign of increased susceptibility to developing VOD, though this theory should be tested in a prospective study.

Although in all our patients Act-D was always given with vincristine, VOD is likely to be a side-effect of Act-D, as demonstrated by the fact that a reduction of Act-D doses and changes of its administration schedules have been shown to decrease the incidence of this complication [9–13]. Moreover, Raine and colleagues reported that using protocol UKW3 for stage 1 Wilms' tumour which includes vincristine, but not Act-D, no cases of VOD were observed [10]. Vincristine was given with no complications to 1 of our patients after resolution of VOD.

It has been reported that VOD after Act-D develops mainly in patients with right-sided Wilms' tumour and it has been suggested that it may be due to the consequence of mechanical obstruction of the hepatic venous outflow [22,23]. All 4 patients with Wilms' tumour in our series did in fact have a right-sided lesion, but in 3 the tumour had been removed well before the presentation of VOD. Whether the presence of a large mass or the absence of a functioning kidney is responsible for VOD remains uncertain. The incidence of VOD appears to be less when similar doses of Act-D are given to treat tumours not affecting the kidney, such as rhabdomyosarcoma (Table 5) [14].

Prevention and best management of VOD remain to be determined, especially in children. Currently, the medical management is primarily supportive, as detailed in Table 4. Patients with VOD are usually fluid overloaded, but intravascularly depleted. Supportive treatment should be aimed at reducing the extravascular overload by restricting the fluid intake, giving diuretics, and maintaining a good oncotic pressure with colloids. We have used octreotide and propranolol to reduce portal hypertension and gastrointestinal bleeding. Broad-spectrum antimicrobials and N-acetylcysteine were given as part of our standard treatment of liver failure [42]. Despite supportive treatment, the mortality in our series is high, with two children dying during the acute phase of the disease and one of tumour recurrence, possibly due to delayed chemotherapy because of the severity of VOD. Although liver transplantation has

been performed successfully in severe VOD [43], the respiratory and renal impairment of our patients precluded this mode of treatment.

Our data do not allow us to provide firm guidelines for drug reduction to avoid severe VOD. The right balance between risk of VOD and risk of tumour recurrence is difficult to establish and better left to the oncologist. However, we believe that the Act-D dose should be reduced after an episode fulfilling the clinical criteria for the diagnosis of VOD and that the drug should not be used again after an episode of VOD with multi-organ involvement. The role of what is referred to in this paper as 'early isolated thrombocytopenia' in deciding a dose reduction of Act-D needs to be confirmed in a larger series.

In conclusion, multi-organ failure associated with VOD after Act-D is closely related with the development of intravascular coagulopathy and appears to be predicted by the occurrence of isolated thrombocytopenia during previous treatment courses, suggesting that intravascular coagulopathy plays an important pathogenic role. The prognosis of VOD involving kidneys and lungs is poor and treatment unsatisfactory.

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