Pediatr Nephrol (1998) 12: 284–289

Pediatric Nephrology

Original article

Vincristine and focal segmental sclerosis: do we need a multicentre trial?

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Received September 1, 1997; received in revised form December 12, 1997; accepted December 15, 1997

Abstract. Over the last 10 years, eight children have received vincristine for the treatment of steroid- and cyclophosphamide-resistant nephrotic syndrome at Great Ormond Street Hospital for Children, London. We present our experience of these eight cases and put forward a case for reassessing the effectiveness of vincristine in this disorder. In our series, two children treated with vincristine achieved complete remission with preserved renal function, including relapses in one. Both had primary steroid- and cyclophosphamide-resistant focal segmental glomerulo sclerosis (FSGS). Of the other cases, four also had primary FSGS, one familial FSGS and one mesangioproliferative glomerulonephritis. We discuss in general the pros and cons of vincristine therapy in nephrotic syndrome versus the cytotoxic agents that are currently used and the differences in clinical features among the responders and non-responders in this small group. In addition, we explore why this may have occurred and summarise the literature over the last 25 years, where vincristine appeared to have been beneficial, especially in secondary forms of nephrotic syndrome associated with malignancy. We conclude that vincristine therapy warrants re-examination as it could be a valuable alternative therapeutic agent in some cases of FSGS with relatively minor side effects.

Key words: Focal segmental glomerulosclerosis – Vincristine therapy

Introduction

Most cases of primary nephrotic syndrome in childhood have minimal change histology and more than 90% will respond to steroid therapy [1, 2]. Among the non-responders, 25% or more have focal segmental glomerulosclerosis (FSGS) and half will progress to end-stage renal failure, which constitutes about 10% of cases of end-stage renal disease in children [3–5]. Although children tend to have a better prognosis than adults [2], some 30% will require dialysis and transplantation within 5 years of diagnosis [6].

FSGS is a heterogeneous clinico-pathological entity and may occur in many settings [7]. Its pathogenesis may vary, since not only can it be primary, but also familial [8, 9] or associated with other genetic disorders such as Cockayne and Schimke syndromes [10, 11]. The familial form that follows an autosomal recessive pattern of inheritance has been linked to chromosome 1q25-q31 [12]. It is more common and more severe in black populations [13] and may recur post renal transplantation [14, 15]. It is unpredictable in its response to therapy and this may well be reflective of its multiple aetiologies [16].

Primary FSGS has no demonstrable cause and there are no universally accepted morphological or clinical criteria for the diagnosis. The presence of tubulointerstitial lesions and widespread capillary loop collapse on renal biopsy are generally thought to be associated with a poor prognosis [17, 18], whereas mesangial proliferation may be indicative of a more favourable outcome [19]. Glomerular immune complex deposition does not usually occur, and when present does not necessarily define a distinct clinicopathological entity [20].

Of the primary glomerulopathies that cause nephrotic syndrome, FSGS is the most resistant to therapy with glucocorticoids and cytotoxic agents [9, 21, 22], although a small number of patients experience spontaneous remission or respond to glucocorticoids. Alkylating agents, specifically cyclophosphamide and chlorambucil, are used widely in FSGS as an alternative to, or in combination with, glucocorticoids, despite their poor efficacy in children who have shown resistance to glucocorticoid treatment [23]. Azathioprine and vincristine have also generally been considered to be ineffective [24], although there are a few reports of success with vincristine [25]. The response to cyclosporin was initially encouraging with a remission rate of 30% in some series [26, 27], although some report this

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effect to be short-lived [27–30], although features such as premature withdrawal or inadequacy of cyclosporin dosage might have played a part. At present, of all reported regimens, a protocol combining intravenous methylprednisolone pulses, alternate-day prednisolone and an alkylating agent has produced the highest percentage of sustained remissions (66% of cases) with stable renal function [31, 32]. However, this high response rate is yet to be reproduced by other centres.

Apart from a few case reports [25, 33, 34], anecdotal evidence suggests that vincristine is ineffective in primary FSGS, although it may sometimes confer therapeutic benefit, particularly in cases of FSGS secondary to malignancy [35–37]. We report two patients (cases 1 and 2) with primary FSGS who have responded to vincristine therapy alone, with no deterioration of renal function to date. In addition, we summarise our experience of vincristine therapy for childhood nephrotic syndrome at Great Ormond Street Children's Hospital, London, over the last 10 years.

Case reports

Case 1

A previously healthy Caucasian girl presented at the age of 15 months with a 2-week history of oedema. She had heavy proteinuria, ascites, raised blood pressure (115/95 mmHg) and raised plasma creatinine (134 μmol /l). She was apyrexial, had normal serum complement and a negative autoantibody screen. There was no family history or drug therapy. Her nephrotic syndrome was treated initially with intravenous albumin, high-dose prednisolone (60 mg/m^2 per day) and penicillin V prophylaxis. Proteinuria and nephrotic syndrome continued. A renal biopsy showed variable degrees of mesangial proliferation and segmental glomerulosclerosis. An 8-week course of cyclophosphamide (3 mg/kg daily) was commenced and steroids were slowly reduced and discontinued. She achieved a partial remission (i.e., asymptomatic but continuing low-grade proteinuria) within 2–3 weeks of commencing cyclophosphamide. The blood pressure normalised (96/73 mmHg), renal function improved (creatinine 30 μmol/l) and proteinuria continued to reduce slowly to a urine albumin/urine creatinine ratio (Ua/Ucr) value of 3–4. At this stage at 2 years of age, her nephrotic syndrome relapsed (Ua/Ucr 18, plasma albumin 24 g/l) and was treated with prednisolone and cyclophosphamide (3 mg/kg daily for 8 weeks). Because of a poor response (persisting symptoms and proteinuria), weekly pulsed intravenous vincristine (1.5 mg/m^2 for 8 weeks) therapy was added. She improved clinically with this treatment, although continued to have mild proteinuria (Ua/Ucr 1–3) which diminished with time, eventually reaching a Ua/Ucr <1, at 4 years of age. At the age of 7 years, she relapsed and responded well to a further 8 weeks of weekly vincristine alone. At the age of 7 years and 10 months, she relapsed again and a second renal biopsy showed 20 glomeruli, of which 6 showed varying degrees of segmental hyalinosis and sclerosis with scanty IgM and C1q deposition. On this occasion only a partial remission could be achieved after eight doses of weekly vincristine (Ua/Ucr 1.0). She was therefore maintained on a vincristine dose every 2 weeks initially, reducing gradually to a pulse of vincristine every 5–6 weeks, extending to 3–4 months. With the longer gaps, some proteinuria re-emerged towards the time of the injections, but settled after a dose of vincristine. Vincristine was finally discontinued at the age of 11.5 years during which time her proteinuria had ceased. She remained well subsequently but relapsed again at the age of 15.5 years, fully responding to an 8-week course of vincristine alone.

Case 2

A previously healthy Caucasian boy aged 2 years and 11 months presented with nephrotic syndrome which was resistant to therapy (6 weeks) with prednisolone 60 mg/m^2 per day. The renal biopsy showed mild mesangial hypercellularity with a slight increase in mesangial matrix in some glomeruli, a few glomeruli with segmental areas of tuft sclerosis and occasional foci of tubular atrophy. There were no immune deposits. A diagnosis of FSGS was made and he was treated with an 8-week course of cyclophosphamide (3 mg/kg per day) with added dipyridamole and diuretics (spironolactone and frusemide). Oedema disappeared but proteinuria continued. Thereafter, a course of vincristine (1.5 mg/ m^2 per week, 8 doses) was given, to which he responded gradually over 4–5 weeks. He has not relapsed in 6 years of follow-up. Neither of these cases showed any adverse effects of vincristine.

Discussion

Despite extensive chemical and experimental investigations, the pathogenesis of primary FSGS remains undefined and this contributes to the difficulties experienced in trying to treat this disease successfully. Moreover, response to therapy is unpredictable [16], and successful pharmacological therapy of the nephrotic syndrome does not necessarily accompany morphological resolution of renal changes or alter the risk of progression to renal failure [6]. Primary FSGS is the likely result of the interplay of a number of pathogenic factors which converge in the final common pathway of glomerulosclerosis and tubulointerstitial disease. Based on experimental studies [38] and on observations made in human kidney biopsy material [39], there is circumstantial evidence that the podocytes (visceral epithelial cells) may be primarily involved. These show swelling, vacuolisation, protein storage and focal detachment from the underlying glomerular basement membrane (GBM), the resulting space being filled with cell debris and new matrix material [39]. More recently it has been shown that this loss of adhesiveness to the GBM may be the result of severe abnormalities in the distribution of podocyte cytoskeleton associated proteins, such as actin and integrins, as well as proteins such as laminin and type IV collagen expressed by the GBM [40].

Vincristine is a vinca alkaloid and has played an important role in the chemotherapy of malignant disease for 3 decades. It blocks mitosis and produces metaphase arrest. Its oral absorption is unpredictable and therefore it is only administered intravenously. The anticancer potential of vincristine was discovered coincidentally when extracts of the plant *Vinca rosea* (*Cartharanthus roseus*) were noted to cause myelosuppression in rats and subsequently shown to have antitumour activity in mice. Vincristine is a classical spindle poison binding to the microtubular protein tubulin and arresting cell division during the metaphase via microtubular stabilisation. In vitro studies suggest that binding of vincristine to specific sites prevents the polymerisation of tubulin to form microtubules and induces depolymerisation of microtubules that have already formed. Polymerisation and depolymerisation of tubulin is a complex and well-controlled process involving the binding of GDP, GTP and microtubule-associated proteins [41, 42]. The beneficial effects of vincristine in nephrotic syndrome,

Table 1. A summary of children with nephrotic syndrome who received vincristine therapy in combination with other immunosuppressive agents during the last 10 years at our institution

Age (years) at onset	Renal histology	Treatment before vincristine	Combined medication with vincristine	Before VCR GFR (P_{CT}) P_{cr} Ua/Ucr	After VCR GFR (P_A) P_{cr} Ua/Ucr	Final outcome
Case 1 1.5	Primary FSGS	Prednisolone, cyclophosphamide	Frusemide, penicillin	GFR 72 P_a 1.5 Ua/Ucr 13.2	GFR 70 P_{cr} 43 Ua/Ucr 2.9	Remission – 3 relapses also responding completely[a]
Case 2 4	Primary FSGS	Prednisolone, cyclophosphamide	Frusemide, dipyridamole, penicillin	GFR 109 P_a 18 Ua/Ucr 8.4	(P_{cr} 20) P_a 31 Ua/Ucr 1.7	Remission[a]
Case 3 2.5	Familial FSGS (IgM and Cl_q deposits)	Prednisolone, cyclophosphamide	Frusemide, spironolactone, penicillin	GFR 48 (P_{cr} 66) P_a 12 Ua/Ucr 25	GFR 19 (P_{cr} 68) P_a 14 Ua/Ucr 26	Renal transplant
Case 4 5	Primary FSGS	Prednisolone, cyclophosphamide	Spironolactone, penicillin, frusemide	GFR 15 (P_{cr} 157) P_a 15 Ua/Ucr 3.5	(P_{cr} 181) P_{cr} 29 Ua/Ucr 9.1	Renal transplant
Case 5 14	Primary FSGS	Prednisolone, cyclophosphamide	Frusemide, penicillin, spironolactone	GFR 47 (P_{cr} 104) P_a 22 Ua/Ucr 27.6	(P_{cr} 136) P_a 17 Ua/Ucr 6.4	No response
Case 6 9	Primary FSGS (IgM and C 3 deposits)	Prednisolone cyclophosphamide	Frusemide, spironolactone, penicillin, dipyridamole	GFR 71 (P_{cr} 34) P_a 8 Ua/Ucr 143.0	(P_{cr} 20) P_a 18 Ua/Ucr 12.5	Reduced proteinuria
Case 7 4.5	Mesangioproliferative glomerulonephritis	Prednisolone, cyclophosphamide, pulsed methylprednisolone	Frusemide, spironolactone, penicillin	(P_{cr} 106) P_a 6 Ua/Ucr 27	(P_{cr} 166) P_a 6 Ua/Ucr 18	Renal transplant
Case 8 1.3	Primary FSGS (IgM deposits)	Prednisolone, cyclophosphamide, cyclosporin A	Penicillin, prednisolone	GFR 93 (P_{cr} 47) P_a 7 Ua/Ucr 4.3	(P_{cr} 41) P_a 28 Ua/Ucr 2.5	No response

VCR, A course of intravenous vincristine weekly for 8 weeks; P_a, plasma albumin (g/l); GFR, glomerular filtration rate (ml/min per 1.73 m^2); P_{cr} plasma creatinine (μmol/l), Ua/Ucr, urinary albumin creatinine ratio (mg/mg); FSGS, focal segmental glomerulosclerosis
[a] After a period of proteinuria remission achieved

particularly when associated with haematological malignancy, have been noted for many years [43–51]. This latter group of patients is, however, heterogeneous and only some have histological features of FSGS underlying the nephrotic syndrome. The pathogenesis of the nephrotic syndrome in this situation is unknown, but most patients show a good response to therapy, which usually consists of a combination of various cytotoxic agents, steroids and vincristine. It is unclear whether the high remission rate is related to suppression of the underlying tumour or some direct effect on the nephrotic syndrome.

The response to vincristine in primary FSGS, as in our cases, could be due to a direct effect of this agent upon the podocyte cytoskeleton. Very recently, the modulation of cytoskeleton organisation of podocytes has been examined by immunoelectron microscopy during the course of puromycin-induced nephrosis in rats [52]. In control rats, the cytoplasmic filaments tubulin and vimentin in particular were limited to the podocyte cell body and major processes, but not the foot processes. Myosin exhibited the same distribution, whereas actin was scattered over the fibrillar zones of the cell body and its processes, including the foot processes. In proteinuric rats, loss of foot processes occurred and the GBM was covered by broad cytoplasmic sheets of podocytes, which contained these four units of cytoplasmic filaments. With disappearance of proteinuria, the structural organisation of the foot processes was completely restored, in which tubulin, vimentin and myosin were scarcely observed. Loss of foot processes, therefore, appeared to be caused by the retraction of cytoplasmic filaments (tubulin, vimentin and myosin) and their specific localisation in the podocyte contributes to the maintenance of a particular cell shape [52]. Vincristine, therefore, may be involved in restoration of the lost podocyte cytoskeleton in these nephrotic cases.

There are only limited reports in the literature on the use of vincristine in childhood primary FSGS [25, 33, 34]. In all cases, the response has been variable and in each situation vincristine has been administered in combination with either cyclophosphamide and prednisolone [33] or prednisolone alone [25]. Our two patients were white Caucasian and had primary FSGS on renal biopsy at the time of initial diagnosis. Both had established resistance to prednisolone and cyclophosphamide therapy at standard dosages prior to commencement of vincristine. There was no demonstrable family history of nephrotic syndrome and both had normal renal function at the beginning of treatment. The response to treatment was notable at 1 month. Case 1 relapsed after initial treatment but the relapses also consistently responded to vincristine with no evidence of resistance, and renal function was preserved long term. Case 2 has not relapsed since his first course of vincristine 6 years ago,

Table 2. A comparison of the immunosuppressive agents used in the treatment of FSGS-associated nephrotic syndrome

	Vincristine	Cyclophosphamide	Cyclosporin A	Chlorambucil
Chemical structure	Vinca alkaloid	Alkylating agent	Fungal metabolite	Alkylating agent
Mode of action	Interferes with microtubule assembly causing metaphase arrest	Interferes with cell multiplication by damaging DNA	T cell suppression	Acts by damaging DNA
Administration	IV only	Oral	Oral	Oral
Cumulative toxic dose	Not described	Not described (500 mg/kg for azospermia)	Not described	>18 mg/kg causes azospermia but <10 mg/kg does not
Serious side effects at the recommended dose for nephrotics	Peripheral and autonomic neuropathy (reversible) Syndrome of inappropriate secretion of antidiuretic hormone	Haemorrhagic cystitis Severe effects on gametogenesis Risk of acute non-lymphocytic leukaemia	Dose-dependent renal dysfunction Hypertension Neurological complications Lympho proliferative disease	Marrow suppression Severe rashes Toxic epidermal necrolysis Stevens-Johnson syndrome
Dose and frequency of therapy	1.5 mg/m^2 per week 8 doses	3 mg/kg per day for 8 weeks	5 mg/kg per day for at least 1 year	0.2 mg/kg per day for 12 weeks
Efficacy for treatment of FSGS	Not known	Recommendation recently withdrawn [23]	30%–35% partial or complete remission [26, 54]	Not known

and also shows normal renal function long term. These case reports are unique in that they are the first published demonstrations of steroid-resistant nephrotic syndrome secondary to idiopathic childhood FSGS responding to vincristine when used as the sole therapeutic agent. This therapeutic response is in contrast to the experience we have had with other patients with FSGS treated with vincristine (Table 1), which raises two questions: why did these children respond and is there any useful information that we can gain from them?

So why did these children respond? Unfortunately, our experience of vincristine when used for the treatment of primary FSGS, parallels that of other centres in demonstrating that there were no significant differences between those patients with primary FSGS that did respond to vincristine and those that did not. Of our six patients that did not respond, however, only three had true primary steroid-resistant FSGS (one subsequently responded to cyclophosphamide), one patient had an initial diagnosis of steroid-responsive minimal change disease that converted after 6 years to steroid-resistant FSGS and responded to chlorambucil, one had familial FSGS and one mesangioproliferative glomerulonephritis. In addition, all had moderate-to-severe renal impairment before commencement of vincristine therapy, whereas in the two that did respond vincristine was started early in the course of the disease (with a near-normal renal function) rather than as a salvage procedure.

At the molecular level, drugs used in the treatment of primary FSGS have very diverse mechanisms of actions (Table 2). Again the mechanism of action of vincristine at the cellular level does not give any concrete clues as to why it might be beneficial in FSGS. It is possible that if binding to tubulin with resultant metaphase arrest is the mechanism of action in primary FSGS, the differing inheritance of tubulin, which does not necessarily produce an abnormal protein but determines the type and specificity of vincristine binding, may have a part to play in the clinical effect.

Despite the more-promising results of combination therapy with intravenous methyl-prednisolone pulses, alternate-day prednisolone and an alkylating agent [31], primary FSGS in childhood continues to pose a therapeutic dilemma. Despite anecdotal evidence to the contrary, this paper illustrates that vincristine in certain situations may prove beneficial. With current chemotherapeutic options there will always be a group of children with primary steroid-resistant FSGS that will not respond to any sort of therapy and will inevitably progress into chronic renal failure. Although vincristine may not necessarily be able to help children within this group, its use may be appropriate in some steroid- and cyclophosphamide-resistant patients. Additional advantages are the lack of a cumulative toxic dose, no nephrotoxicity and no serious irreversible side effects, such as sterility, as seen with cyclophosphamide. Newer vinca alkaloids, such as vinorelbine tartrate, may even be superior in this respect [53]. Our limited data also suggest that vincristine may be more appropriate used early (as first- or second-line rather than the last option when all other treatments have failed) rather than late (i.e. when much permanent renal damage has occurred) in the course of the condition. Furthermore, it is our experience that a response will be observed in 1 month or less, which may prove helpful in judging whether a child is likely to benefit from the treatment, perhaps preventing longer courses of non-beneficial therapy. The convenience of administration as a weekly intravenous dose with diminishing frequency is a further advantage, specifically in groups where compliance may be a problem, for example, adolescents. Consequently we propose that the therapeutic effects of vincristine in the context of primary FSGS (and may be even in steroid-resistant minimal change disease) in childhood needs further exploration, since it may have a more important role in the treatment of this condition than has hitherto been thought.

Acknowledgements. C.D.A.G. was supported by John Herrings and Friends Fund (Child Health Research Appeal Trust). A.B.K. is a Turistington Higgins Fellow supported by National Kidney Research Aid Fund. S.A.H. was supported by Caring For Kids Fund (Child Health Research Appeal Trust) at the time these data were collected.

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Literature abstract

Transplantation (1997) 63: 1263–1267

Risk factors for vascular thrombosis in pediatric renal transplantation: a special report of the North American Pediatric Renal Transplant Cooperative Study

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Vascular thrombosis remains a major cause of graft failure, accounting for 12.2% of failed index transplants and 19.2% of repeat transplants. We conducted a special study to identify the risk factors for vascular thrombosis. A total of 4394 transplants (2060 living donor [LD] transplants and 2334 cadaver donor [CAD] source transplants) were evaluated. The respective vascular thrombosis rates for LD and CAD transplants were 38/2060 (1.8%) and 100/2334 (4.2%) ($P < 0.001$).

Univariate analysis showed that the rate of graft loss due to thrombosis was significantly higher in younger children (less than 2 years of age) as compared with older age groups (2–5 years, 6–12 years, and more than 12 years of age) (9.0% vs. 5.5%, 4.4%, and 3.5% for CAD transplant recipients and 3.5% vs. 3.4%, 0.7%, and 1.9% for LD graft recipients). Recipients of kidneys from cadaver donors less than 5 years of age had a significantly higher thrombosis rate (8.3%) than did recipients from older donor groups (5–10 years, 4.5%; greater than 10 years, 3.2%). Recipients of kidneys with cold ischemia time greater than 24 h also had a higher thrombosis rate (5.6%), as compared with recipients of kidneys with a shorter cold ischemia time (3.2%). Recipients of antilymphocyte therapy on day 0 or day 1 were at dimished risk of graft loss due to thrombosis (2.2% vs. 4.1%, $P = 0.001$). Comparable trends were seen for both LD and CAD organ recipients. LD organ recipients with a history of prior transplantation had a significantly higher rate of thrombosis as compared with those who received a primary transplant (4.6% vs. 1.6%, $P = 0.005$). For both LD and CAD organ recipients, the occurrence of acute tubular necrosis was a significant risk factor for the development of thrombosis.

Regression analysis showed that for LD organ recipients, a history of prior transplantation increased the risk for thrombosis, whereas increasing recipient age had a linear decreasing risk effect. The use of antilymphocyte antibody or cyclosporine on day 0/1 decreased the risk for thrombosis. For CAD kidney recipients, organ cold ischemia time greater than 24 h increased the risk for thrombosis. The use of antibody induction therapy, donors greater than 5 years of age, and increasing recipient age were factors that decreased the risk for thrombosis.