Chlorambucil therapy in children with steroid-resistant nephrotic syndrome

Jameela A. Kari, *FRCPCH, FRCP (UK),*
Abdulmohsen Alkushi, *MSc, FRCPC,*
Hammad O. Alshaya, *FRCPCH, FRCP(UK).*

Chlorambucil (CHL) had been used as treatment for childhood nephrotic syndrome (NS) for more than half a century.[1] It was used mainly in children with steroid sensitive nephrotic syndrome (SSNS) as steroid sparing agent in those with frequent relapsing or steroid dependent course.[2] However, it was observed to result in higher rates of severe side effects and recommended as a second line drug after cyclophosphamide (CYC), which is considered as safer alkylating agent.[2] The alkylating agents have been used for treating steroid resistant nephrotic syndrome (SRNS).[2] However, CYC was used in most of the studies,[3] while CHL was used only rarely.[4,5] Elzouki et al showed in a small study that CHL induced complete or partial remission in patients with SRNS caused by either focal segmental glomerulosclerosis (FSGS) or mesangial proliferative glomerulonephritis (MPGN).[4]

In this retrospective study, we report our results of using CHL in children with SRNS secondary to IgM nephropathy, FSGS or diffuse mesangial hypercellularity (DMH). All patients presented to our unit over 20 months period (from February 2002 until June 2004) and were diagnosed as SRNS were recruited. Steroid resistant nephrotic syndrome was defined as a failure to go into remission after 4 weeks of prednisolone therapy at a dose of 60 mg/m^2 /day, plus 3 intravenous doses of methylprednisolone (600 mg/m^2/day or 30 mg/kg/day) on alternate days. We had 7 patients with SRNS. All patients were females. The median (range) age at presentation was 4 (2-9) years. All except 2 were Arab in origin. All studied children were primary non-responders to prednisolone and 2 were also resistant to intravenous cyclophosphamide course. All the 7 children were treated with CHL (0.1-0.2 mg/kg/day) for 8-12 weeks. The mean ± SD accumulative dose was 10.1 + 3.3 (7.0-15.2) mg/kg. All patients were continued on oral prednisolone 40mg/m^2 on alternate days and received enalapril (0.5-1 mg/kg) throughout the CHL therapy. Two patients achieved complete remission after 12 weeks of CHL therapy. One patient remained in remission for 2 years following CHL therapy and one patient had a relapse once after 1.5 years of follow up, which responded to prednisolone promptly. She had been on one year remission. Two patients received CYC of 500 mg/m^2 per month for 6 doses before CHL therapy. The rest of the patients did not respond after 8 weeks of CHL therapy (**Table 1**). All of them except one were treated subsequently with Cy A. Two patients achieved complete remissions on Cy A while one patient achieved partial remission only. One patient was treated with CyA initially as the histopathology showed FSGS. However, she was treated with CHL when she showed sign of CyA toxicity and achieved

Table 1 - Laboratory data before and after chlorambucil therapy in individual patients.

Patient's no.	Age at onset (years)	Sex	Histo-pathology	Pre-therapy			Duration of therapy (weeks)	Accumulative dose (mg/kg)	Post-therapy		
				S. alb (g/l)	S.cr (umol/l	Urine protein			S. alb (g/l)	S.cr (umol/l	Urine protein
1	4	F	IgM nephropathy	19	21	3+	12	14	37	22	-ve
2	2.5	F	IgM nephropathy	6	20	3+	12	15.2	38	24	-ve
3	2	F	DMH	4	19	3+	8	10.3	6	10	3+
4	5	F	IgM nephropathy	23	13	3+	8	8.6	24	11	2+
5	3.5	F	IgM nephropathy	15	31	3+	8	7.3	19	35	3+
6	7.5	F	IgM nephropathy	10	41	3+	8	8.5	10	68	3+
7	9	F	FSGS	21	85	3+	8	7	29	55	2+

F - female, IGM - ???, DMH - diffuse mesangial hypercellularity, FSGS - focal segmental glomerulosclerosis, S.alb - serum albumin, S.cr - serum creatinine, -ve = negative

partial remission after 8 weeks. No side effect was observed in any of the patients. None of the patients had leucopenia, hemorrhagic cystitis, infection, vomiting or alopecia. Our finding suggests that CHL is of therapeutic value in inducing remissions in children with SRNS secondary to IgM nephropathy. This agrees with previous reports of using it in SRNS caused by other histopathological forms.[4,5] Pascual et al reported that CHL is effective in SRNS caused by MCD5 and Elzouki et al reported that CHL induced complete remission in 3 out of 4 patients with FSGS.[4] One patient in this study experienced partial remission and one patient with SRNS caused by MPGN achieved complete remission. The 2 children who achieved complete remission in our study received 12 weeks course of CHL and higher accumulative dose (15.2 and 14mg/kg) than the non-responders who received 8 weeks course with a lower accumulative dose. We did not observe any side effects in our patient. However, CHL is known to cause many side effects.[2] Leucopenia occurs in approximately one of 3 patients receiving CHL and infection in 6.3%.[2] Children who received CHL are also at increased risk of developing malignancies (approximately 0.6%). However, the reported cases received longer duration and higher total accumulative total dose.[2-4] The Gonadal toxicity is also a risk with CHL therapy particularly in males.[2] It was estimated that CHL at a dose of 17 mg/kg with concomitant steroid may be safe.[2] However, the risk is minimized with a total dose of 7-10 mg kg. Seizures were also reported in 3.4-8% of children treated with CHL.[2]

We conclude that CHL therapy in a total accumulative dose of 15 mg/kg and 12 weeks duration could achieve complete remission in children with SRNS secondary to IgM nephropathy. Further randomized controlled studies are required.

Received 25th September 2005. Accepted for publication in final form 3rd January 2006.

From the Departments of Pediatrics (Kari, Alshaya) and Pathology (Alkushi), King Abdul-Aziz University Hospital, Jeddah, Kingdom of Saudi Arabia. Address correspondence and reprint requests to: Dr. Jameela Kari, Department of Pediatrics, King Abdul-Aziz University Hospital, PO Box 80215, Jeddah 21589, Kingdom of Saudi Arabia. Tel. +966 55677904. Fax. +966 (2) 6732410. E-mail jkari@doctors.org.uk

References

1. Leveque B, Debauchez C, Deflandre L, Marie J. [Chlorambucil in the treatment of idiopathic nephrotic syndrome without glomerular lesions in childhood. Apropos of 30 cases] Le chlorambucil dans le traitement du syndrome nephrotique idiopathique sans lesion glomerulaire, chez l'enfant. A propos de 30 observations. ***Ann Pediatr (Paris)*** 1969; 16: 13-23.
2. Latta K, von Schnakenburg C, Ehrich JH. A meta-analysis of cytotoxic treatment for frequently relapsing nephrotic syndrome in children. ***Pediatr Nephrol*** 2001; 16: 271-282.
3. Alshaya HO, Al-Maghrabi JA, Kari JA. Intravenous pulse cyclophosphamide-is it effective in children with steroid-resistant nephrotic syndrome? ***Pediatr Nephrol*** 2003; 18: 1143-1146.
4. Elzouki AY, Jaiswal OP. Evaluation of chlorambucil therapy in steroid-dependent and cyclophosphamide-resistant children with nephrosis. ***Pediatr Nephrol*** 1990; 4: 459-462.
5. Pascual JF, Molina M, Lopez J. Long-term assessment of chlorambucil in children with nephrotic syndrome who fail to respond adequately to corticosteroids. ***Contrib Nephrol*** 1981; 27: 65-74.

Dear Author, please read through your article carefully, make a critical review and highlight any changes you require to be made, please also list these clearly on a separate sheet. Please pay particular attention to all authors names under the title of the article, the running title and the footer of the first page. Please also check the accepted and received dates in this footer. Please carefully check all legends to figures and all column headings in tables, ensuring that total numbers in tables are correct and correspond to results in the text of your article. Please also pay particular attention to the spelling of all medical and non medical words throughout your article

This is extremely important as mistakes not corrected prior to publication can cause embarrassment, more so to the authors than the publisher. After you have signed and returned the galley proof of your article, the Journal will not be held responsible for any errors that appear in the final print. Although erratum notices may be published, this will only be carried out when the error is the fault of the publisher and not the author

Please then sign on each and every page of your manuscript and return it to our office together with an indication of whether you wish to order re-prints of your article (see below).

Please do not hesitate to call if you have any further queries.

Many thanks.

OFFPRINTS REQUIRED YES ☐ NO ☐
(Please tick relevant box)

MS# 20051035

IF YES IS TICKED THEN PLEASE ENSURE THAT YOU COMPLETE THE ENCLOSED OFFPRINT FORM OTHERWISE OFFPRINTS CANNOT BE ORDERED