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ALKYLATING AGENT TREATMENT IN CHILDREN WITH STEROID-RESISTANT NEPHROTIC SYNDROME IN WEST JAVA

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ABSTRAK

Abstract:
Objective: to evaluate SRNS therapy in children. Steroid-resistant nephrotic syndrome (SRNS) is one of the most common causes of chronic kidney disease in children. Kidney Disease Initiative for Global Outcome (KDIGO) no longer recommends an alkylating agent (AA) as the treatment protocol for SRNS, still in some developing countries, such as Indonesia, there are some limitations in obtaining immunosuppressive agents other than AA. Method: Data were collected from the medical records of SRNS children with SRNS aged between 1 and 18 years from January 2016 to December 2021. The data included time to remission, adverse effects, and relapse-free period after receiving AA treatment based on the lesion type. Results: Among the 369 patients enrolled from January 2016 to December 2018, 244 patients (66.12%) had remission with AA, and 125 patients experienced persistent proteinuria. Most of them had remission during the fifth to seventh cycles of intravenous AA (after 6 – 8 months). None of the patients experienced severe adverse effects of AA. Only a small proportion of patients had chronic kidney disease (CKD) stage II–V during follow-up. Conclusions: AA is still effective in treating SRNS in children, with only a few and less harmful adverse effects.

***Abstrak*:**
Pendahuluan: Penelitian bertujuan untuk mengevaluasi terapi sindrom nefrotik resisten steroid pada anak. Sindrom nefrotik resistan steroid (SNRS) merupakan salah satu penyebab tersering penyakit ginjal kronik (PGK) pada anak. Kidney Disease Initiative for Global Outcome (KDIGO) tidak lagi merekomendasikan agen alkilasi (AA) sebagai protokol pengobatan untuk SRNS, tetapi di beberapa negara berkembang, seperti Indonesia, terdapat beberapa keterbatasan dalam memperoleh agen imunosupresif selain AA. Metode: Data dikumpulkan dari catatan medis anak dengan SNRS berusia antara antara 1 dan 18 tahun dari Januari 2016 hingga Desember 2021. Pengumpulan data meliputi waktu remisi, efek samping, dan periode bebas kambuh setelah menerima pengobatan AA berdasarkan jenis lesi. Hasil: Dari 369 pasien yang terdaftar dari Januari 2016 hingga Desember 2018, 244 pasien (66,12%) mengalami remisi dengan AA, dan 125 pasien mengalami proteinuria persisten. Sebagian besar dari mereka mengalami remisi selama siklus kelima hingga ketujuh AA intravena (setelah 6 – 8 bulan). Tidak ada pasien yang mengalami efek samping AA yang parah. Hanya sebagian kecil pasien yang mengalami PGK stadium II–V selama masa tindak lanjut.Ke simpulan: AA masih efektif dalam mengobati SRNS pada anak-anak, dengan hanya sedikit efek samping yang tidak terlalu berbahaya.

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INTRODUCTION

Steroid-resistant nephrotic syndrome (SRNS) is a disease that contributes to chronic kidney disease in children. We need an alternative therapy to steroids to handle it. Some ofalternative immuno-suppressive (IS) treatments are alkylating agents (cyclophosphamide, chlorambucil) [1-3].

Most SRNS in children is focal segmental glomerulosclerosis (FSGS), which has a better prognosis than the others.[4], [5] The Kidney Disease Initiative for Global Outcome (KDIGO) recommends calcineurin inhibitors as the treatment protocol for SRNS, not AA, but in some developing countries, there are some limitations in obtaining immuno-suppressive agents other than AA. To overcome the limitations of drugs that should be given for SRNS, namely Calcineurin inhibitors, AA is still given in developing countries. Management of SRNS is challenging, with the goals to induce remission, minimize complications, and thromboembolism, and restrict drug toxicity[6].

Managing SRNS in developing countries is challenging, as there is a gap between the drug and its availability. The drug recommended by KDIGO to treat SRNS is a calcineurin inhibitor (cyclosporine A and tacrolimus), but unfortunately, we have some trouble with the feasibility of this drug, notably due to national insurance coverage. In the present study, we demonstrated the outcomes of SRNS with various lesions caused by AA treatment.

This study aims to determine the results of SRNS treatment using AA, and whether the potential risk of side effects that may be experienced by children corresponds to the results obtained. There has been a lot of research on the outcomes of children with SRNS in developed countries where side effects are monitored well, but in developing countries and low socioeconomic countries, it is still not well published.

RESEARCH METHOD

The subjects enrolled in this study were children with SRNS from the pediatric ward and outpatient clinic from January 2016 to December 2021. Before being diagnosed with SRNS, patients were treated with prednisone or methyl-prednisolone for 4–8 weeks. Patients who experienced steroid toxicity, such as moon face, hypertension, hyperglycemia, striae, and hirsutism, were enrolled for 4 weeks with only 60 mg/m2 daily prednisone. Patients without steroid toxicity were enrolled with 8 weeks of 60 mg/m2 daily prednisone.

After the determination of SRNS, the patients were administered 40 mg/m2 steroid on alternate days with intravenous 500–750 mg/m2 cyclophosphamide simultaneously. The cyclophosphamide is given once monthly until seven cycles; the prednisone is given an alternate dose of 40 mg/m2 a day. The patients were monitored for any vomitus, hypertension, anaemia, leukopenia, thrombocytopenia, and any infectious disease, whether it was the most common complication of nephrotic syndrome. All patients were advised to visit the outpatient clinic at least monthly to monitor clinical improvement, comorbid conditions, and adverse effects of the drugs.

The patient who did not show some clinical improvement was suggested to undergo a kidney biopsy. The research was conducted with permission from the Ethics Committee of Padjadjaran University No 1030/UN6.KEP/EC/2021.

RESULT AND DISCUSSION

Among 369 patients consisting of 248 males and 121 females enrolled consecutively from January 2016 to December 2021, 244 (66.12%) had remission with AA, and 125 (33.88%) did not achieve remission. Focal segmental glomerulosclerosis was observed in 82.7% of the cases, with the rest being membranoproliferative glomerulonephritis (MPGN), mesangial proliferative nephritis,

and focal global glomerulonephritis. Most patients (58.79%) had remission during the fourth to sixth months of CPA treatment (Table 1). None of the patients experienced the severe adverse effects of CPA. Only a small proportion of patients had chronic kidney disease stage II–V during follow-up. The histopathologic findings (Table 2) of the patient were mostly focal segmental glomerulosclerosis (FSGS), and only a small part with membranoproliferative glomerulonephritis (MPGN); all of the remission cases had FSGS. Only 133 (36.04%) children agreed to undergo kidney biopsy.

Table 1.
Profile of SRNS patients treated with AA

Characteristics	Male (%)	Female (%)	Total (%)
Age (year)			
1-7	186 (50.4)	60 (16.26)	246 (66.67)
8-18	62 (16.80)	61 (16.53)	123 (33.33)
Total	248 (67.21)	121 (32.79)	369 (100)
Remission achievement (month of AA)			
first	3 (0.81)	0	3 (0.81)
second	5 (1.35)	0	5 (1.35)
third	6 (1.63)	3 (0.81)	9 (2.44)
fourth	5 (1.36)	8 (2.17)	13 (3.5)
fifth	34 (9.21)	22 (5.96)	56 (15.18)
sixth	33 (8.94)	34 (9.21)	67 (18.16)
seventh	35 (12,92)	46 (12.47)	81 (21.95)

AA, alkylating agent

Table 2.
Histopathologic profile of SRNS

Histopathologic	Male (%)	Female (%)	Total (%)
FSGS	77 (57.89)	33 (24.81)	110 (82.71)
MPGN	15 (11.28)	4(3.01)	19 (14.29)
Mesangial proliferative diffuse	0	4(3.01)	4 (3.01)
N	92 (69.17)	41 (30.83)	133 (100%)

FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis

The present study demonstrated that Cyclophosphamide (CPA) is still effective in treating steroid-resistant nephrotic syndrome (SRNS), in line with the Sepahi et al study.[7] Kidney Disease Initiative for Global Outcome (KDIGO) recommends CPA as steroid-dependent nephrotic syndrome and frequently relapsing nephrotic syndrome, but does not recommend CPA for SRNS anymore.[6] The data suggest that CPA is as effective and safe as SRNS. However, both studies have some limitations, i.e. they are both forced to use AA due to limited funds as developing countries. This study and Sepahi et al's study also did not carry out monitoring of side effects on gonadal function in a cohort form.

The problem in developing countries such as Indonesia is in a low economic state, so national insurance is helping the people. National insurance is still developing, with limited drug coverage and laboratory examinations. CPA is the only drug that can be safely administered by pediatric nephrologists to treat SRNS. We can adequately monitor for adverse effects such as anaemia, leukopenia, thrombocytopenia, and neutropenia, with simple laboratory examination. Most of the histopathologic results in this study were FSGS (table 2); therefore, the drugs chosen should be CNIs. Giving AA to them is only because of limited facilities.[6] National insurance also covers calcineurin inhibitors (CNIs), that is, cyclosporine A (CyA) as the first-line drug recommended by KDIGO for SRNS treatment, but unfortunately, treatment with CyA requires blood CyA monitoring for effective and safe treatment; national health insurance still has not yet covered that examination.

The patient who was treated with AA had a good result (table 1); the onset of remission was about 5–6 months, and the duration of remission after AA and steroid discontinuation was 4 months to 5 years. The side effects were nausea only after AA administration (61 %), alopecia (1.5 %), infection (5.6 %), absence of hemorrhagic

cystitis, bone marrow suppression, hypertension, hypertrichosis, nephrotoxicity, or gum hyperplasia. The infections that occurred included subacute bacterial peritonitis, cellulitis, hospital-acquired pneumonia, sepsis, and diarrhoea.

The results of this research cannot be compared with other studies, because currently other countries no longer use AA, and only some developing and low socioeconomic countries still use AA, with the results not being well published. CPA is a synthetic nitrogen mustard AA with antineoplastic and immunosuppressive properties. In the liver, CPA is converted to active metabolites, including phosphoramide mustard, which binds and crosslinks DNA and RNA, thereby inhibiting DNA replication and protein synthesis. Low doses of CPA have potent immunosuppressive effects, primarily by depleting T regulatory cells. This agent is associated with minor transient serum enzyme elevation and has been linked to rare cases of acute liver injury. A high dose of CPA can cause acute sinusoidal obstruction syndrome.[8], [9]

AA destroys the DNA of target cells and is thought to exert cytotoxicity through the cross-linking of cellular DNA. This agent also inhibits embryonic DNA synthesis and does so before its effect on RNA or protein synthesis, producing DNA cross-links, and other DNA lesions or as well, mediates Go/G1 and S phase arrest.[10]

The results also did not include patients with acute liver injury or sinusoidal obstruction syndrome related to AA. However, nine adolescent patients experienced delayed puberty. Most of the patients had a good quality of life because they were able to have activities as good as other children. Although AA is no longer the drug of choice for SRNS, it can still be an alternative therapy in developing countries where calcineurin inhibitors or monoclonal antibodies are not available. The risk of gonad toxicity must be monitored. This study shows that AA still has a fairly good impact on children with SRNS, but cohort studies are needed to monitor reproductive function in the future. Further studies linking the duration of AA with gonadal function are needed. The present study had some limitations, that is, it did not measure gonadal function. Appropriately, AA should not be administered for a long duration because of its side effects of gonadotoxicity. The administration of CNIs (tacrolimus or cyclosporine A) while monitoring CNI levels in the blood remains the standard that should be carried out in every country, including developing countries.

CONCLUSION

Alkylating agents may still be used as the mainstay of therapy for the management of SRNS in countries with limited facilities, i.e. with difficulties in obtaining calcineurin inhibitors (cyclosporine A, tacrolimus, or monoclonal antibodies (rituximab), with strict monitoring of side effects, especially gonadotoxicity. The AA remission rate is still much lower than the drugs currently recommended by KDIGO (cyclosporine A, tacrolimus, or rituximab).

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