In addition, other side effects have been reported and are as follows: excessive inhibition of bone metabolic turnover, resulting in the suppression of the longitudinal growth of bone, and decreased bone strength due to inhibition of bone remodeling [51]. Use of bisphosphonates requires careful attention and the indication should be applied only to patients with nephrotic syndrome after the period of adolescence, as those patients do not have concern for their growth. Comprehensive consideration for efficacy and safety should also be dictated in these patients. Administration of bisphosphonates to patients with renal impairment is not recommended. For therapeutic strategies for nephrotic syndrome in children after the growth phase, guides from the "The Japanese Guidelines for the Prevention and Treatment of Osteoporosis, 2011" and "Guidelines on the Management and Treatment of Glucocorticoid-Induced Osteoporosis, 2004" should be followed. The package inserts of bisphosphonates describe: "bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of weeks to years" and "should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus." Bisphosphonates should be administered carefully to women in the transitional phase.

Activated vitamin D3 has been reported to have efficacy on the prevention for vertebral body fractures in adults. In children, a randomized, controlled study in patients with pediatric nephrotic syndrome, including relapsing cases, indicated that administration of vitamin D and calcium preparations at the initiation of steroid therapy suppressed the decrease of bone mineral density [56]. However, the study also demonstrated a significant increase in serum and urine calcium levels, suggesting a higher risk for hypercalciuria and urolithiasis. This evidence is insufficient due to the small sample size, and efficacy and safety of vitamin D3 in children have not yet been established. Also not yet established is the efficacy and safety for the use of vitamin K, selective estrogen receptor modulator, and parathyroid hormone.

4. Reduction and discontinuation of steroids

There is no sufficient evidence on medical treatments for steroid-induced osteoporosis in patients with pediatric nephrotic syndrome. Presently, the reduction or discontinuation of steroids is recommended for the treatment of steroid-induced osteoporosis. Immunosuppressants other than steroids should be used as applicable in patients with frequently relapsing or steroid-dependent nephrotic syndrome. Reduction or discontinuation of steroids is also recommended for the prevention of steroid-induced osteoporosis.

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Chapter 5. Side effect of steroids: growth deficiency

Recommendation statements:
1. Alternate-day administration of steroids reduces the risk of growth deficiency (short stature) and thus we recommend it as applicable. [Recommendation grade B]

Explanation

Growth deficiency in patients with pediatric nephrotic syndrome is one of the most important side effects of long-term use of steroids. Height growth is affected by endochondral bone growth in the direction of the long axis. Steroids directly suppress chondrocyte maturation on the epiphyseal growth plate, which inhibits the endochondral bone growth, leading to growth deficiency. Steroids also inhibit the secretion of growth hormone and activity of insulin-like growth factor 1 (IGF-1) at the epiphyseal growth plate, causing growth deficiency.

Daily administration of steroids has been involved in inducing growth deficiency. It has been reported in patients who received daily administration of steroids for renal disease or kidney transplantation, an improvement in growth deficiency by switching to alternate-day administration [57, 58]. Although focusing primarily on steroid therapy following kidney transplantation, these studies have demonstrated the efficacy of alternate-day administration of steroids for relief of growth deficiency [58–61]. Since the 1970s,

alternate-day administration of steroids has been carefully studied as a useful method for alleviating several complications of steroid use, including growth deficiency in pediatric renal diseases [62]. However, except for growth deficiency, any other usefulness has not yet been clearly established. Although an improvement of growth deficiency has not been observed in all children treated with alternate-day administration of steroids, a significant improvement in growth deficiency in children treated with alternate-day administration of steroids after kidney transplantation has been reported, as compared to those treated with a daily administration of steroids [58]. Another published report suggests that alternate-day administration of steroids prevents patients with diseases other than renal disease (i.e. juvenile idiopathic arthritis) from any onset of growth deficiency [63]. Therefore, it is considered that alternate-day administration of steroids is beneficial for the improvement of growth deficiency.

With respect to dosage amount that may lead to growth deficiency in patients with pediatric nephrotic syndrome, one report concluded that a 6-month administration course of prednisolone at, or more than 0.75 mg/kg/day (converted dosage per day), was associated with the development of growth deficiency [64]. Another study estimated the yearly growth rates of patients with growth deficiencies following the administration of prednisolone over 3 years for asthma or pediatric nephrotic syndrome; this study showed that, in patients who continued treatment with prednisolone at or more than 0.35 mg/kg/day, growth hormone treatment did not improve the growth rate [65]. Steroid therapy, even at low doses, induces growth deficiency in a dose-dependent manner based on the duration of treatment. Thus, in patients with pediatric nephrotic syndrome who require long-term steroid therapy, steroid dosage should be reduced or discontinued as soon as possible by using immunosuppressants such as cyclosporine to avoid growth deficiency [59].

Alternate-day administration of steroids is effective in alleviating growth deficiencies complications from steroid therapy in patients with pediatric nephrotic syndrome. Most major guidelines, including KDIGO guidelines and Cochrane reviews, have espoused the alternate-day administration of steroids as the basic therapeutic strategy, and, in patients with renal diseases, the dosage of steroids after induction of remission should be reduced to alternate-day administration.

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Chapter 6. Side effect of steroids: ophthalmologic complications

Recommendation statements:
1. We suggest an ophthalmologic examination early on after the commencement of steroid therapy to lower the risk of steroid-induced glaucoma. [Recommendation grade C1]
2. We suggest regular ophthalmologic examinations during steroid therapy to detect steroid-induced cataract formation in the early phases and to lower the risk of any cataract progression. [Recommendation grade C1]

Explanation

Major ophthalmologic complications with steroid therapy include glaucoma and cataract formation. It has not been demonstrated that early ophthalmologic examinations can significantly lower the risk of glaucoma and cataracts. Previous studies reported that 10–56 % of children with renal disease, and treated with steroids, developed cataracts [66–73]. With respect to glaucoma, some studies found no increase in intraocular pressure; [72, 73] however, other studies reported an increase of intraocular pressure in 20 % of the patients [71, 74]. This variation in results is attributable to different timing of examination.

1. Glaucoma

Steroid-induced glaucoma develops as a result of raised intraocular pressure due to steroid therapy and, when left untreated, leads to impairment of optic nerves and visual (field) disturbances. At the beginning of high-dose steroid therapy, intraocular pressure may be elevated in the early phase, and in most cases, then decreases as the steroid therapy is reduced or discontinued [71]. However, one study reported a case with ocular hypertension that had elevated intraocular pressure after cessation of steroid therapy, and the patient had to undergo a trabeculectomy. This result therefore suggests the need to be cautious during and following steroid treatment [71]. Ocular hypertension can be improved by ophthalmic solutions with early detection and avoidance of continuous ocular hypertension can halt any progression of optic nerve disorders. Early ophthalmologic examinations are preferred.

There is no consensus on adequate timing for ophthalmologic examinations following steroid therapy. In general, it is preferable to visit an ophthalmologist during the time when a stable general condition has been achieved and

with an improvement in edema by the steroid therapy. In patients with relapsed nephrotic syndrome and a history of steroid-induced ocular hypertension specifically, where patients require high-dose administration such as steroid pulse therapy, then early examinations, including intraocular pressure measurements, are necessary. Patients developing symptoms of glaucoma, such as ocular pain, headaches, and decreased vision, should be referred to an ophthalmologist as soon as possible.

2. Cataracts

Steroid-induced cataracts often present as posterior subcapsular cataracts. The onset rate of posterior subcapsular cataracts does not appear to have a significant association with dose volume or steroid therapy, [66–69] suggesting that steroid sensitivity may be responsible. [69] Kobayashi et al. and Hayasaka et al. [70, 71] reported that dose volume and steroid therapy duration are both associated with the rate of formation of cataracts. In general, use of prednisolone at or more than 10 mg/day or long-term treatment (more than 1 year) is accompanied by an increased onset of cataracts. Multiple ophthalmic solutions for cataracts are available, but the number of randomized, controlled studies are limited; accumulation of further evidence is warranted. Patients receiving long-term, high-dose therapy may require surgery for reduced visual acuity due to opacity of the lens. Although there is no obvious rationale for recommending early ophthalmologic examinations after steroid therapy, regular ophthalmologic examinations enable physicians to assess any complications as well as any potential progression of cataracts at the early stage, where the usage of steroids and immunosuppressants would be considered.

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Chapter 7. Immunization and infection control

Recommendation statements:

1. Patients with nephrotic syndrome are considered immunocompromised. Since acquired infection may lead to severe disease in such patients, we therefore suggest immunizations be performed, when applicable. [Recommendation grade C1]
2. We suggest that vaccination with inactivated vaccines be considered even during steroid and immunosuppressant treatment. [Recommendation grade C1]
3. In general, we suggest live attenuated vaccines not be used in patients during steroid or immunosuppressant treatment. [Recommendation grade C2] However, the decision to use attenuated vaccines may be determined on a case-by-case basis and according to the condition of the patient and epidemic. [Recommendation grade C1]
4. When any family member of the patient does not have a history or has not been vaccinated against the prevalent infection, we suggest proactive vaccination to the family member. [Recommendation grade C1]
5. In cases where the household has been in close contact with varicella, we recommend prophylaxis with antiviral drugs (acyclovir or valaciclovir). [Recommendation grade B]
6. In cases of long-term, high-dose therapy with steroids or immunosuppressants, we suggest use of prophylactic antibiotics be carefully considered by a specialist. [Recommendation grade C1]

Explanation

1. Vaccination of patients with nephrotic syndrome

Patients with nephrotic syndrome are immunosuppressed due to severe hypoproteinemia, including immunoglobulin, and thus are susceptible to infections, which can easily become severe [75–79]. Annual mortality rates for patients with pediatric nephrotic syndrome were as high as 20 % before steroids became indicated for the disease. Most of the cases died from bacterial infections, which appeared to

develop at the time of recurrence and were further complicated with severe hypoalbuminemia or edema. The dominant type of nephrotic syndrome is steroid-sensitive, minimal change nephrotic syndrome. Since steroids came into use for the treatment of the disease, hypoalbuminemia and edema can be immediately controlled and the mortality rate from infection has dramatically decreased. However, in cases with steroid-dependent or -resistant disease, long-term treatment with steroids cannot be avoided, and immunosuppressants are then used to circumvent any side effects of steroid treatment. Such patients are still considered immunocompromised and at high risk of developing severe infections. Therefore, infection control in patients with nephrotic syndrome is an important management target and performing vaccinations is recommended, when applicable [75–79].

In Japan, vaccinations administered to immunodeficient individuals, including patients with nephrotic syndrome, were conventionally withheld for the following possible reasons: lower antibody acquisition rate and acquired antibody value when compared against healthy children, shorter duration of acquired antibody, and risk of infection by the activation of any given attenuated virus.

Accumulating knowledge based on domestic and international studies suggests that, in patients with nephrotic syndrome not using steroids or immunosuppressants, routine vaccinations that are legally required (DPT, Hib, pneumococcal, measles, rubella, and Japanese encephalitis vaccines) and commonly performed (varicella, mumps, influenza, and hepatitis B vaccines) are effective and can be safely provided [79–85].

Note that for recently approved vaccines of human papillomavirus, inactivated poliovirus, and rotavirus, the efficacy and safety in immunodeficient patients, including those with nephrotic syndrome, have not been fully established, even worldwide.

Information, such as the necessity of vaccinations, their timing, and their availability according to the treatment and type of vaccine, is unlikely to be conveyed to the patients and their families. For example, the partial amendment to the Preventive Vaccination Act in January 2013 made pediatric nephrotic syndrome and focal glomerular sclerosis applicable to these preferential measures, which permits vaccination within 2 years, after the dissolution of excluding factors for vaccination to certify as legally required routine vaccinations. Providing the families of patients with full access to this information about such vaccinations is required.

2. Inactivated vaccinations to patients with nephrotic syndrome

Accumulating domestic and international evidence, from small studies and foreign guidelines that incorporate such data, suggests that, in patients with nephrotic syndrome not using steroids or immunosuppressants, inactivated vaccinations are effective and can be safely provided.

Pneumococcus is the most common cause of bacterial infections observed in patients with nephrotic syndrome. The predominance has not been changed even after the start of steroid usage. Pneumococcus causes peritonitis and sepsis, which are the major causes of death in patients with the disease [76–78]. Immunocompromised patients are susceptible to pandemic influenza, which can easily become severe. In guidelines published by the Centers for Disease Control and Prevention and KDIGO, the 7- or 23-valent pneumococcal vaccines and yearly influenza vaccine are recommended. [79–84] The efficacy of 7- and 23-valent pneumococcal vaccines has been previously reported in patients with nephrotic syndrome. Vaccination using the 23-valent pneumococcal vaccine in patients treated with high-dose prednisolone (60 mg/m^2/day) has been reported to have comparable efficacy to that in patients treated with low-dose, alternate-day steroid administration [80, 81]. In Japan, vaccination of both 7- and 23-valent pneumococcal vaccines is approved. The 7-valent pneumococcal vaccine with an adjuvant effect is indicated in children between the ages of 2 months and 9 years, and commonly, three additional vaccinations have been completed by the time they are 15 months old. The indication of the 23-valent vaccine, a polysaccharide vaccine, is in children greater than 2 years-old. The duration of effect is shorter than that of the 7-valent vaccine, which requires a booster vaccination after 5 years in immunocompromised patients, including the elderly. These vaccines thus require differential use in accordance to the age of the patients. Note that the indication of the 23-valent vaccine is for immunocompromised patients, including those with nephrotic syndrome and chronic kidney disease; however, only splenectomized patients are covered by health insurance in Japan.

Our guidelines do not include vaccination with pneumococcal vaccines, based on the current situation in Japan. However, in patients with nephrotic syndrome who are at high risk for severe pneumococcal infections, including peritonitis and sepsis, vaccination with pneumococcal vaccines is recommended as early as possible, as stated in foreign guidelines [79–82].

3. Vaccination using live attenuated vaccines to patients with nephrotic syndrome

The safety and efficacy of vaccination using live attenuated vaccines (BCG, measles, varicella, rubella, mumps, and rotavirus) in immunocompromised patients has not been established. Immunocompromised patients using steroids or immunosuppressants have been known to be susceptible to varicella and are at risk for increased severity [76]. Guidelines published in the United States and Europe recommend vaccination based on reports regarding the safety and efficacy of the vaccination of varicella in patients treated with low-dose steroids [85]. Patients during

treatment with high-dose steroids (converted dose in prednisolone, >2 mg/kg/day; or in children weighing ≥10 kg, ≥20 mg/day) should not be vaccinated.

For the safety and efficacy of vaccination using live attenuated vaccines in patients during treatment with immunosuppressants, definitive evidence has not been established. Immunosuppressants available in Japan are contraindicated to the use of live attenuated vaccines, as stated in the package inserts. The vaccination should be avoided until 3 months following the discontinuation of immunosuppressants. In cases where the benefit of the vaccination is considered to outweigh the disadvantages, in terms of the condition of the patient and pandemic (for example, patients with progressive renal dysfunction due to steroid-resistant nephrotic syndrome that may undergo transplantation or dialysis), vaccination using live attenuated vaccines may then be considered.

4. Prevention of intra-familial infection

Close contact with family members, specifically contact with infected siblings, is associated with the highest risk for transmission of infection in children. In cases where there is a family member without any history of vaccination and living together with a patient treated with steroids or immunosuppressants, we recommend that the family member be vaccinated, when applicable. Specifically, for varicella [76, 85] and influenza [83], vaccinations should be proactively administered.

5. Prophylaxis in cases of close contact to varicella

In cases where patients with lowered immunity come into close contact with varicella, or where varicella is within the household, guidelines in the United States recommend vaccination with varicella-zoster immunoglobulin. This vaccination, however, is not implemented in Japan. Prophylactic use of acyclovir has been reported to be effective [86]. In cases where children at high risk for severe infection have been in close contact with varicella patients, prophylaxis using acyclovir of 80 mg/kg/day, divided into four doses, or valacyclovir of 60 mg/kg/day, divided into three dose for 7 days and 7–10 days after the contact, is recommended, according to a report by the American Academy of Pediatrics [86].

6. Other infection control strategies

Immunosuppressants such as cyclophosphamide and cyclosporine have been increasingly used in patients with refractory (steroid-dependent and -resistant) nephrotic syndrome. There are no published studies directly targeting patients with nephrotic syndrome under treatment with immunosuppressants and thus the prevalence of infection due to use of immunosuppressants in patients with nephrotic syndrome has not yet been determined. There is also not enough sufficient evidence concerning the efficacy of immunoglobulin or antibiotics as prophylaxis in patients with severe hypoimmunoglobulinemia or immunosuppression. However, in studies that have been performed on collagen diseases and organ transplantations, treatment with immunosuppressants or high-dose steroids is associated with the frequent occurrence of severe complications, including Pneumocystis pneumonia. In cases of prolonged nephrotic syndrome and an immunosuppressed state, prophylactic use of immunoglobulin or antibiotics (i.e., sulfamethoxazole/trimethoprim) may be considered under the consultation of a specialist. Use of immunosuppressants requires considerable caution as excessive immunosuppression by overdose can occur, and proper administration by a specialist is preferred.

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Chapter 8. Transition

Recommendation statements:
1. We suggest that supportive programs be implemented in cooperation with other departments from the early phases of nephrotic syndrome, in consideration of the childhood to adult transition. [Recommendation grade C1]

Explanation

1. Implementation of supportive programs of transition

(1) Rate of transition

Nephrotic syndrome appears to increase during the transition from childhood to adult. When alkylating agents, such as cyclophosphamide, were commonly used as immunosuppressants in patients with frequently-relapsing and steroid-dependent nephrotic syndrome, the rate of transition of idiopathic nephrotic syndrome developed in childhood into adulthood (at or more than the age of 18) was 5–10 % [87, 88]. Recently, with increasing use of calcineurin inhibitors such as cyclosporine, the transition rate has increased to 33–42.2 % [89, 90]. As mentioned in section 7 in part 1 of this guideline, consideration for the childhood-adult transition is needed at the onset of nephrotic syndrome.

(2) Support to transition

Transition is defined as "a process that involves purposeful, planned efforts to prepare the pediatric patient to move from caregiver-directed care to disease self-management in the adult unit." Supportive programs have recently been established to achieve this transition. The programs can be divided into six sections as follows: self-support, independent health care, sexual management, psychological support, educational/occupational plan, and health and lifestyle. Systematic support in these sections enable a patient to fit into the responsibilities of adulthood regardless of the disease and to transition without any problems. Implementation of the supportive programs cannot be performed only by physicians and requires cooperation from the paramedical staff. However, improvements to the current environment are still needed to facilitate such cooperation. The number of institutions that have implemented supportive programs is limited and thus educational activity to healthcare providers should be promoted. A consensus statement by the International Society of Nephrology (ISN) and the International Pediatric Nephrology Association (IPNA) was published in 2011, proposing the TRxANSITION Scale which consists of 10 checkpoints. The statement put forward the importance of an individualized process that also allows for the conditions of the patients, family, and local custom.

Japan is behind other western countries in both research and practice of the childhood-adult transition. Programs implemented in the United States and Europe may be referred to; however, the establishment of programs adapted to the medical context and characteristics in Japan is considered important. The creation of an individualized support system is currently in progress.

(3) Economic burden after transition

An economic challenge with the childhood-adult transition is that the clinical course may worsen due to refraining from the use of expensive drugs, since the medical aid program for chronic pediatric diseases of specified categories in Japan is terminated at the age of 20 [91].

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ORIGINAL ARTICLE

Renal biopsy criterion in idiopathic nephrotic syndrome with microscopic hematuria at onset

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Abstract
Background The criterion for performing a renal biopsy in children with idiopathic nephrotic syndrome (NS) showing microscopic hematuria at onset remains controversial.
Methods To determine an adequate renal biopsy criterion in children with NS showing hematuria, the optimal cutoff for the maximum red blood cell (RBC) range in urine sediment to separate minimal change disease (MCD) from other glomerular changes was obtained by receiver operating characteristic analysis. We studied 29 children with NS showing hematuria who were screened from 1,320 patients who underwent renal biopsies between January 2001 and September 2011. Patients were divided into two groups according to the cutoff value to verify its validity.
Results The optimal maximum RBC range was 30–49/high-power field (HPF). In group 1 (RBC ≤29/HPF, n=14), 3 patients showed nephritis and the other 11 patients showed MCD. In group 2 (RBC ≥30/HPF, n=15), 1 patient showed focal segmental glomerulosclerosis, 12 showed nephritis, and the other 2 showed MCD. These findings indicated that the ratio of non-MCD/MCD was significantly higher in group 2 than in group 1 (P<0.01).
Conclusions The use of maximum RBC range (30–49/HPF) for a criterion of renal biopsy in patients with NS showing hematuria may be reasonable for clinical practice.

Keywords Minimal change disease · Focal segmental glomerulosclerosis · IgA nephropathy · Membranoproliferative glomerulonephritis · Receiver operating characteristic analysis

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Introduction

Idiopathic nephrotic syndrome (NS) is defined as NS in the absence of systemic disease. This category is divided into two types of entities according to histopathological findings: minimal change disease (MCD) and other glomerular changes. Idiopathic NS is the most common type of childhood NS, representing more than 90 % of cases between 1 and 10 years of age and 50 % after 10 years of age [1]. Most NS patients have histological findings of MCD, and the vast majority of patients with MCD (>90 %) respond to steroid therapy [2]. Based on these observations, an initial trial of steroid therapy is generally administered to children who are likely to have MCD based on a clinical diagnosis, avoiding renal biopsy. Renal biopsies carried out before the initiation of therapy are recommended when children with idiopathic NS show continuous hematuria, hypertension, elevated serum creatinine levels, hypocomplementemia, or are less than 3 months of age, because these signs also suggest other diseases besides MCD [1, 3].

Although continuous hematuria is an indication for renal biopsy in children with idiopathic NS, the optimal cutoff of the red blood cell (RBC) count in urine sediment to separate

MCD from other glomerular changes remains unknown. Therefore, we attempted to determine an adequate maximum RBC count in urine sediment as a criterion for renal biopsy in children with idiopathic NS.

Materials and methods

Patients

The study protocol was approved by the regional research ethics vetting boards. A total of 1,320 children aged <20 years who had undergone a renal biopsy at one of four centers (Wakayama Medical University Hospital, Kobe University Hospital, Hyogo Prefectural Kobe Children's Hospital, and Himeji Red Cross Hospital) between January 2001 and September 2011 were screened retrospectively. Of the 1,320 patients, 754 underwent an initial renal biopsy, and of these, 237 underwent a renal biopsy because of NS. Patients with systemic diseases, such as Henoch–Schönlein purpura nephritis or systemic lupus erythematosus, hypertension, elevated serum creatinine levels, hypocomplementemia or treatment before a renal biopsy, were excluded from the analysis. All of the patients were at least 3 months of age or older. Finally, 29 patients underwent an initial renal biopsy only because of hematuria with NS at onset (Fig. 1). The criteria for NS were in accordance with the International Study of Kidney Disease in Children (heavy proteinuria, ≥40 mg/h/m^2 and hypoalbuminemia, ≤2.5 g/dl) [4]. Hematuria was defined as five or more RBCs in a properly collected and centrifuged urine specimen under high-power field (HPF, ×400 magnification) [5]. The RBC count in urine sediment was graded as 0, 1–4, 5–9, 10–19, 20–29, 30–49, 50–99, and 100–/HPF according to the method of the Japanese Committee for Clinical Laboratory Standards. According to clinical records, 4 patients underwent a renal biopsy because of continuous positive dipstick findings (≥2+) of occult blood, even with an RBC <5/HPF in the urine sediment. Data from these patients were included for analysis. Each patient's family gave written informed consent to a renal biopsy. Renal tissue was obtained by needle biopsy under ultrasound guidance. Renal biopsy specimens were investigated by routine light, immunofluorescence, and electron microscopy. All biopsy specimens were examined and diagnosed by one of the study investigators (N.Y.). Clinical data and information were obtained from medical records.

Determination of the optimal cutoff point of the maximum RBC count range

First, receiver operating characteristic (ROC) analysis was performed to examine the relationship between the maximum RBC range in the early morning urine sediment during the disease course before a renal biopsy and separation of MCD and other glomerular diseases [6]. The lowest count of each range of RBC in the urine sediment was used for analysis. The optimal cutoff point of the RBC count for a biopsy criterion was calculated using the Youden index [6].

Validity of the optimal cutoff point of the maximum RBC count range

Patients were then divided into two groups based on the optimal cutoff point of the maximum RBC count range in the early morning urine sediment during the disease course before a renal biopsy. Group 1 comprised patients who had a maximum RBC count range less than the optimal cutoff point before a renal biopsy. Group 2 comprised patients who had a maximum RBC count range equal to or greater than the optimal cutoff point at least once during the disease course before a renal biopsy. Histological diagnoses of the two groups at initial biopsies were compared. All of the patients who were analyzed had oral steroid treatment (including combination therapies for nephritis) after a renal biopsy. Responses to treatment at 4 weeks after initiation were investigated to assess the validity of the optimal cutoff point of the maximum RBC count range.

Statistical analysis

The results were analyzed using the JMP version 9 software package (SAS Institute Japan, Tokyo, Japan). The distribution of clinical and morphological attributes between the groups was examined using Fisher's exact test. Continuous characteristics of the groups were compared using the Mann–Whitney U test. A P value of <0.05 was taken as the level of significance.

Results

Determination of the optimal cutoff point of the maximum RBC count range

The number of patients for each maximum RBC count range is shown in Fig. 2. ROC analysis demonstrated that the optimal cutoff point of the maximum RBC count range to separate MCD from other glomerular diseases was 30–49/HPF. The area under the ROC curve was 0.91 (highly accurate; sensitivity was 0.81 and specificity was 0.85, Fig. 3). These findings suggested that the presence of more than 30–49 RBCs/HPF was valid as a renal biopsy criterion for NS with hematuria.

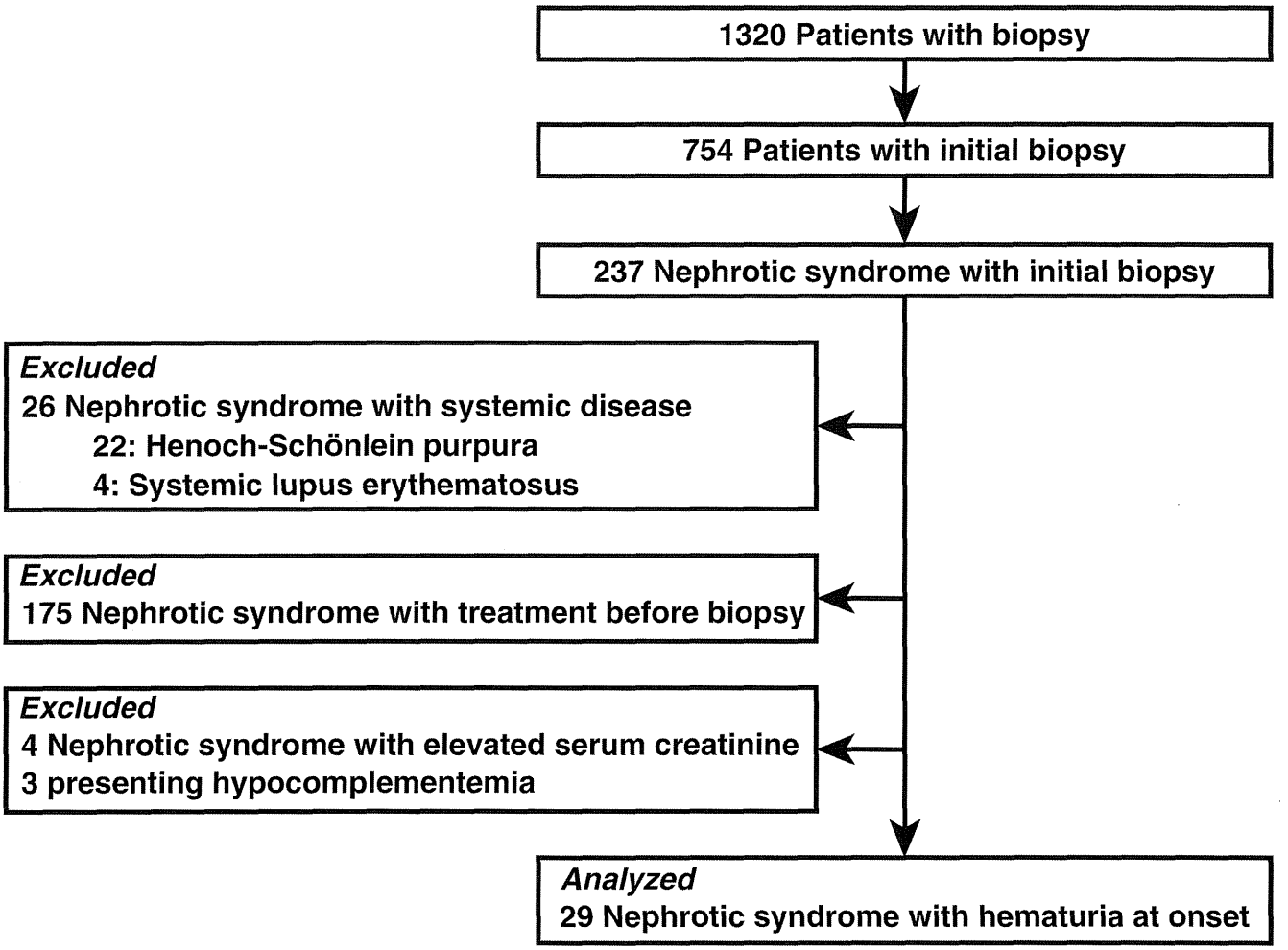

Fig. 1 Patients' profiles

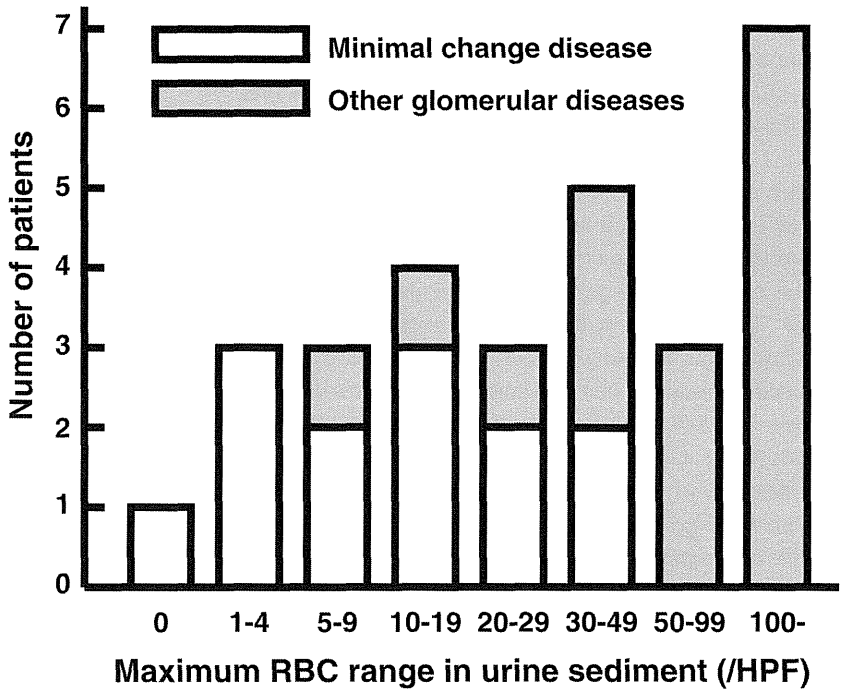

Fig. 2 Number of patients in each maximum red blood cell (RBC) count range

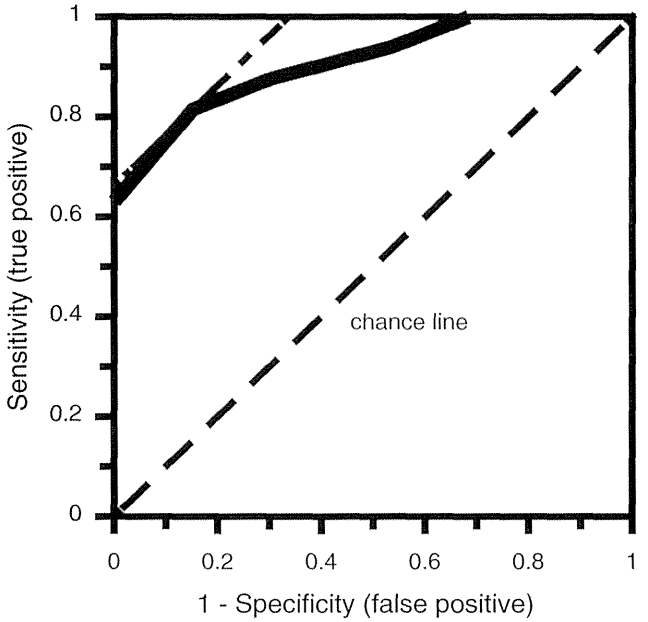

Fig. 3 Receiver operating characteristic (ROC) curve for separating minimal change disease (MCD) from other glomerular diseases. The area under the ROC curve was 0.906. The Youden index is defined as the maximum vertical distance between the ROC curve and the chance line (*dotted line*), and is calculated as maximum (sensitivity + specificity − 1). Using this measure, the cutoff point on the ROC curve, which corresponds to the Youden index, i.e., at which sensitivity + specificity − 1 is maximized, is taken as the optimal cutoff point. For an expedient, the intersection point of the chain line and the vertical axis indicates the Youden index

Validity of the presence of more than 30–49 RBCs/HPF

According to the results of the ROC analysis, 29 patients were divided into two groups based on the maximum RBC range. Group 1 comprised 14 patients who had ≤20–29 RBCs/HPF before a renal biopsy and group 2 comprised 15 patients who had ≥30–49 RBCs/HPF at least once before a renal biopsy. The baseline characteristics in both groups are shown in Table 1. There was no significant difference between the groups, except for the sex ratio (Table 1).

Each specimen in all of the 29 patients contained sufficient glomeruli for evaluation (≥10). The pathological diagnoses are shown in Table 2. In group 1, 11 patients (78.6 %) showed MCD. Two patients with non-IgA mesangial proliferative glomerulonephritis and 1 patient with IgA nephropathy were included in group 1. Their maximum RBC range before a renal biopsy was 5–9 (non-IgA), 10–19 (IgA), and 20–29/HPF (non-IgA). In Group 2, focal segmental glomerulosclerosis was detected in 1 patient and nephritis was detected in 12 patients (non-IgA mesangial proliferative glomerulonephritis, 6; IgA nephropathy, 4; membranoproliferative glomerulonephritis, 2). Two patients (13.3 %) had MCD. Their maximum RBC range before a renal biopsy was 30–49/HPF in both of the patients. The ratio of other glomerular changes versus MCD was significantly higher in group 2 than that in group 1 ($P<0.01$). The maximum RBC range in urine appeared to be a useful criterion for separating other glomerular changes from MCD. There was no significant difference in the ratio of patients with disappearance of proteinuria at 4 weeks after the initiation of treatment between the two groups, both in patients with MCD and those with other glomerular diseases ($P=0.99$, Table 2).

Discussion

Persistent hematuria even microscopic, is an indication for a renal biopsy in children with idiopathic NS. Microscopic hematuria is observed in as many as 20 % of cases in MCD [1]. However, currently, there is no clear criterion for RBC count in urine sediment for a renal biopsy in children with idiopathic NS. An unnecessary renal biopsy in MCD should be avoided. Therefore, our study results could be important for clinical practice.

In the present study, to avoid patient selection bias and to obtain accurate information, we first reviewed all initial renal biopsy cases in the study period. We found that 29 out of 754 (3.8 %) patients had initial renal biopsies only because of hematuria with NS at onset. Although the final number of patients available in the present study is not large (29), data from a 10-year study period should provide useful information.

Our study suggests that the presence of more than 30–49 RBCs/HPF in urine sediment is optimal as a renal biopsy criterion for NS showing microscopic hematuria by ROC analysis with the Youden index. The detection ratio of glomerular diseases of 13 out of 15 (86.7 %), including focal segmental glomerulosclerosis and nephritis, found in group 2 is considered to be appropriate in clinical practice. There were only 3 patients with glomerular diseases in group 1. Some of the patients with glomerular diseases may not undergo renal biopsies according to the criterion suggested in this study. Therefore, even after steroid therapy for NS has been initiated, when an abnormal RBC count range continues, performing a renal biopsy should be considered.

We did not observe a significant difference in the ratio of patients with disappearance of proteinuria at 4 weeks after the initiation of treatment between the two groups in patients with MCD and other glomerular diseases (Table 2). Therefore, the maximum RBC count range in urine sediment was not related to the response to treatments.

Some physicians may think that renal biopsies are unnecessary in patients with NS even showing hematuria if they are steroid-sensitive, because treatments for MCD and non-MCD are not different. However, if we can predict children with other diseases besides MCD by using the optimal cutoff point efficiently, it seems to be reasonable to diagnose by a biopsy and then consider a specific treatment for each disease.

Table 1 Baseline characteristics in the two groups

	Group 1 Maximum RBC range ≤20–29/HPF (n=14)	Group 2 Maximum RBC range ≥30–49/HPF (n=15)	P
Females/males	5/9	11/4	0.04
Age at initial biopsy (years)	7.3±3.9	8.7±4.9	0.38
Duration from first symptoms to renal biopsies (days)	27.2±23.3	24.7±16.6	0.97
Total protein (g/dl)	4.1±0.6	4.4±0.4	0.27
Albumin (g/dl)	1.7±0.6	1.9±0.5	0.17
Blood urea nitrogen (mg/dl)	13.6±6.5	18.2±11.7	0.32
Creatinine (mg/dl)	0.4±0.1	0.5±0.2	0.08
Body weight (kg)	27.8±14.7	26.5±12.2	0.95
Albumin intravenous infusion	7	6	0.72

Data are mean±SD where appropriate

RBC red blood cells, *HPF* high power field

Although microscopic sediment analysis is still used worldwide to examine cells in urine, and the method of urine sediment analysis for the detection of hematuria in this study is the Japanese standard, assessment of microscopic hematuria may vary around the globe depending on the method of collection, analysis or time until analysis [7]. Because of the nature of urinalysis used, we were afraid that we may estimate the optimal maximum RBC count range to be higher than the true value and miss non-MCD with a high frequency. Therefore, it may be reasonable for us to consider adjusting the criterion by one level for the maximum RBC count range so as not to miss glomerular diseases other than MCD. If this is the case, the maximum RBC count range of 20–29/HPF is the optimal cutoff point for a renal biopsy. This option may be reasonable for clinical practice and it appears to be widely accepted by physicians.

This study has several limitations. First, despite our effort to reduce patient selection bias, the retrospective nature of this study may result in such a bias. Second, the low number of patients analyzed is also a limitation. This means that the study may not have been powered, as such, to identify a correlation between number of RBCs and steroid responsiveness. Third, our data have not yet been validated in other cohorts. In order to make specific recommendations for an RBC cutoff for renal biopsy, a multinational, multicenter approach that prospectively examines the outcome of patients who present with nephrotic syndrome with a uniform method of evaluating microscopic hematuria would be ideal. Further evaluation of this criterion in a large-scale cohort is desirable to confirm its validity. The optimal maximum RBC range may need to be adjusted after further evaluation.

Table 2 Pathological diagnosis

Diseases	Group 1 Maximum RBC range ≤20–29/HPF (n=14)	Group 2 Maximum RBC range ≥30–49/HPF (n=15)
MCD	11	2
	8 (72.7 %)	2 (100 %)
Others	3	13
	1 (33.3 %)	5 (38.5 %)
Focal segmental glomerulosclerosis		1
		0 (0.0 %)
Mesangial proliferative glomerulonephritis (non-IgA)	2	6
	1 (50.0 %)	5 (83.3 %)
IgA nephropathy	1	4
	0 (0.0 %)	0 (0.0 %)
Membranoproliferative glomerulonephritis		2
		0 (0.0 %)

Number (ratio [%]) of patients with disappearance of proteinuria at 4 weeks after the initiation of treatment is shown beneath the total number of patients

In conclusion, the current study suggests that use of the maximum RBC range (30–49/HPF) as a criterion for performing a renal biopsy in patients with NS showing hematuria may be reasonable for clinical practice.

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ORIGINAL ARTICLE

Morbidity in children with frequently relapsing nephrosis: 10-year follow-up of a randomized controlled trial

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Abstract
Background To investigate the long-term outcome in children with frequently relapsing nephrotic syndrome (FRNS) we conducted a follow-up of a previous randomized controlled trial (RCT) 10 years after the initiation of the treatment protocol.
Methods We previously conducted an RCT on the efficacy of cyclosporine for treating children with FRNS. After 2 years of treatment, a recommended a management protocol of steroids, and immunosuppressants was provided.
Results Valid information was available for 46 of the 56 patients (82.1 %) enrolled in the original RCT. The median follow-up period was 10.3 years from the start of protocol treatment with cyclosporine. At last follow-up (mean age 18.7 years), only ten patients (21.7 %) showed disease-free remission (no relapse for at least 2 years). In contrast, 23 (50.0 %) continued to relapse frequently or were on immunosuppressants, eight patients (17.4 %) had infrequent relapses without immunosuppressants. Adverse effects attributable to treatment included short stature (6 patients), osteoporosis (six patients), obesity (4 patients), cataracts (3 patients) and hypertension (3 patients). No lethal event or renal dysfunction occurred during follow-up.
Conclusions This 10-year follow-up study shows that most children with FRNS experience relapses after 2 years of cyclosporine treatment, in adolescence and into adulthood. Outcomes in terms of life expectancy and renal function are favorable.

Keywords Children · Follow-up · Long-term · Nephrotic syndrome · Randomized · Controlled trial · Non-remission

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Introduction

The use of immunosuppression therapy in children with frequently relapsing nephrotic syndrome (FRNS), a severe form of nephrotic syndrome which affects about half of patients, has been established [1–5]. Several immunosuppressants, such as cyclosporine and cyclophosphamide, can maintain remission for several years, with a favorable life expectancy and renal survival. Nevertheless, the majority of patients with FRNS experience relapse during long-term care, which may result in serious complications of disease and adverse effects of medications, including impaired growth and decreased quality of life. The clinical consensus that FRNS is a long-term relapsing condition would benefit from further evidence in populations which are better defined.

Several recent studies have reported long-term outcomes of patients with childhood-onset nephrotic syndrome, including FRNS, and shown that long-lasting relapses extend beyond adolescence and continue into adulthood [6–8]. These reports provide important new insights into the long-term nature of nephrotic syndrome, which until that time had generally been considered to spontaneously resolve in early adulthood [9]. However, these studies were conducted as retrospective chart reviews, and populations in two of them were more broadly defined to include those patients with steroid-sensitive nephrotic syndrome (SSNS), of whom typically only about 50 % have FRNS. Further, the severity of relapse at last follow-up was not clearly evaluated. Additional studies in populations which had been better defined would help characterize the long-term outcome of children with FRNS.

We previously conducted a randomized controlled trial (RCT; patient entry 1996–2000) of cyclosporine (Sandimmune®) in a defined population of children with FRNS [10] and established the safety and effectiveness of a 2-year administration of this treatment under trough control. To better understand the long-term outcome of children with FRNS with a well-defined background, we report here the results of our follow-up study of our earlier RCT, approximately 10 years after the initiation of the treatment protocol.

Patients and methods

Previous trial

In the earlier RCT, conducted from January 1996 to January 2000, children with FRNS were treated with cyclosporine (Sandimmune®; Novartis, Basel, Switzerland) [10]. All patients had biopsy-proven minimal change disease. Briefly, the study had a prospective, open-label multicenter design. The criteria for and definitions of nephrotic syndrome, remission and relapse were in accordance with the International Study of Kidney Disease in Children [11]. Patients were randomly allocated into two groups, with both groups initially receiving cyclosporine for 6 months to maintain a whole-blood trough level of between 80 and 100 ng/ml. Over the next 18 months, the dose was adjusted to maintain a slightly lower (60–80 ng/ml) trough level in Group A, while Group B received a fixed dose of 2.5 mg/kg/day, corresponding to a trough level of approximately 20–40 ng/ml. At the 2-year time point, the rate of sustained remission was significantly higher in Group A than in Group B (50 vs. 15 %; p=0.006), and the hazard ratio for relapse was 0.43 in Group A as compared with Group B. On biopsy at the end of the treatment protocol, all patients remained classified as minimal change; mild arteriolar hyalinosis of the kidney was more frequently seen in the children of Group A (n=4) than in those of Group B (n=1), but no patient was diagnosed with striped interstitial fibrosis or tubular atrophy.

Study design

The present study is a retrospective cohort study based on medical records. After 2 years of treatment according to the protocol, cyclosporine was tapered and ultimately discontinued over the following 3 months, after which management was at the discretion of the physician in charge. The following treatment was recommended by the steering committee of the trial: at relapse of nephrotic syndrome, the patient would receive prednisolone 2 mg/kg/day in three divided doses (maximum dose 80 mg/day) for 4 weeks (until 2002) or until remission (from 2002 onwards), followed by a single dose of prednisolone 2 mg/kg in the morning on alternate days for 2 weeks, then 1 mg/kg on alternate days for 2 weeks and finally 0.5 mg/kg on alternate days for 2 weeks. When a patient regressed to FRNS or steroid-dependent nephrotic syndrome (SDNS), those without cyclosporine-induced renal toxicity were re-administered cyclosporine, and those with toxicity were administered cyclophosphamide (2.5 mg/kg/day for 12 weeks).

Follow-up data on status during the 2 years preceding the last observation were collected, with the latest data endpoint being October 2009. Details on the last relapse were also collected, no matter when it occurred. The definitions used in the data collection were:

FRNS	Three or more relapses within any 6-month period (excluding the first 6 months from onset), or four or more relapses within any 12-month period;
SDNS	The occurrence of two consecutive relapses during the tapering of steroid dosage or within 14 days after stopping steroid administration;
Osteoporosis	Bone fracture due to bone mineral loss or a bone mineral density of less than −2SD (standard deviation; age-adjusted) on dual

	energy x-ray absorptiometry (DEXA) [12];
Cataract	as diagnosed by an ophthalmologist;
Glaucoma	increased intraocular pressure, thereby requiring treatment by an ophthalmologist;
Diabetes	A defined by the criteria of the Japan Diabetes Society (http://www.jds.or.jp/e/).

Endpoints and adverse effects

The primary endpoint was the status of nephrotic syndrome relapse and administration of immunosuppressants during the 2 years preceding the last observation. Several status categories were defined in order of approximately decreasing severity, as follows: FRNS/SDNS, as defined above, regardless of the administration of immunosuppressants > major immunosuppression, with the administration of immunosuppressants, including cyclosporine, cyclophosphamide and high-dose mizoribine (≥300 mg/day) for the control of FRNS/SDNS at the last observation > minor immunosuppression, with the administration of regular-dose mizoribine (<300 mg/day) at the last observation > infrequent relapse, with relapse during the last 2 years but not to the extent as to be defined as FRNS/SDNS > disease-free remission, with no relapse for at least 2 years before the time of last observation without immunosuppressants. Patients who fell in more than one of these status categories were placed in the group indicating greater severity.

Adverse effects attributable to the administration of corticosteroids and immunosuppressants as well as complications of nephrotic syndrome were also observed. Renal function was evaluated as the estimated glomerular filtration rate (eGFR), calculated using the abbreviated formula of the Chronic Kidney Disease in Children (CKiD) study [13] [eGFR (ml/min per 1.73 m^2)=0.413 × (height/serum creatinine)], for patients aged≤16 years and the formula for Japanese adults [14] [eGFR=194 × $Cr^{-1.094}$ × $Age^{-0.287}$ (×0.739 if female)] for those aged>16 years.

Statistical analysis

The Mann–Whitney *U* test and Student's *t* test for continuous variables and Fisher's exact test for categorical variables were used. Survival curves for disease-free remission were estimated by the Kaplan–Meier method. A proportional odds model [15] was used to examine the association of relapse during the treatment protocol with cyclosporine, age at onset of nephrotic syndrome, administration of cyclophosphamide before protocol treatment and steroid dependency before protocol treatment, on the probability of relapse. The outcome variable had three levels, namely, low, disease-free remission; medium, infrequent relapse and minor immunosuppression; severe, FRNS/SDNS and major immunosuppression. The underlying assumption in this model is the proportional odds assumption that "the cumulative odds ratio for the covariate is constant across response categories." The model was then used to predict probability as expressed by:

$$\Pr(outcome = Severe) = \frac{\exp(\alpha_1 + \beta_1 X_1 + \ldots)}{1 + \exp(\alpha_1 + \beta_1 X_1 + \ldots)} (\text{intercept1} = \alpha_1)$$

$$\Pr(outcome = Severe \text{ or } Medium) = \frac{\exp(\alpha_1 + \alpha_2 + \beta_1 + X_1 + \ldots)}{1 + \exp(\alpha_1 + \alpha_2 + \beta_1 X_1 + \ldots)} (\text{intercept1} = \alpha_1 + \alpha_2)$$

A two-sided significance level of 0.05 was used. All statistical analyses were performed using the SAS software package for Windows, release 9.2 (SAS Institute Inc., Cary, NC). The previous RCT was registered in the University Hospital Medical Information Network public trials registry (ID C000000014; http://www.umin.ac.jp/ctr/index.htm). Informed consent was obtained from all patients or their parents at the start of the RCT. The design and conduct of this follow-up study were in accordance with the ethical standards laid down in the Declaration of Helsinki and the ethical guidelines issued by the Ministry of Health, Labour and Welfare, Japan. The protocol of the present (follow-up) study was approved by the Ethics Committee of Tokyo Metropolitan Kiyose Children's Hospital (predecessor of Tokyo Metropolitan Children's Medical Center; ID, 21–18).

Results

Patients analyzed

A flow diagram of the study is shown in Fig. 1. Of the 56 patients enrolled in the original RCT, one was lost to follow-up immediately after entry and not included in further analysis, one died due to severe ileus of unknown cause and one was found to be ineligible and excluded from the previous trial because of a history of steroid-resistant nephrotic syndrome (SRNS) before FRNS. Among the remaining 53 patients, four were lost to follow-up just after the original RCT, and follow-up data could not be obtained for a further four patients, while the one patient with a history of SRNS was added to the present analysis (Fig. 1). Our analysis was therefore conducted on a total of 46 patients. Of the 55 patients who received

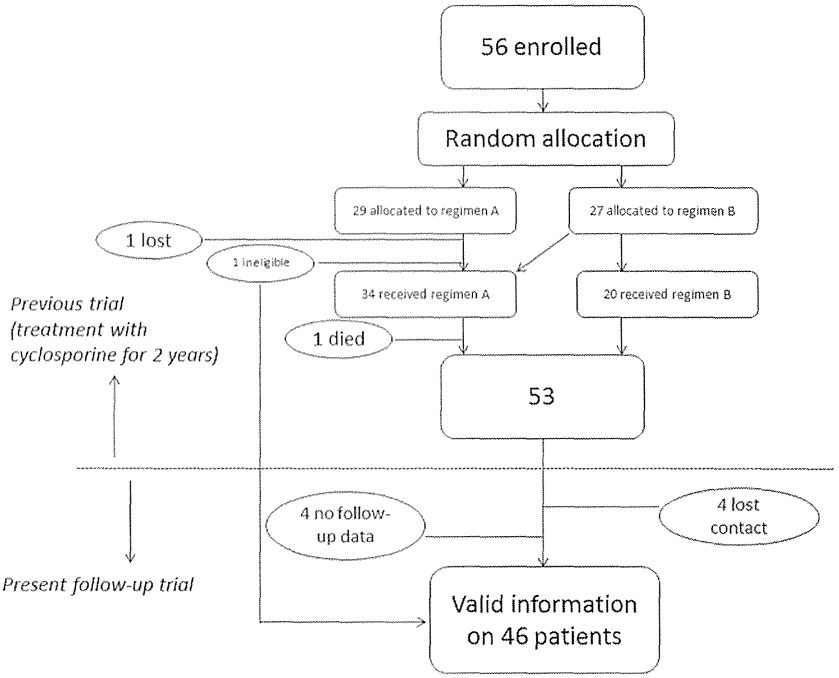

Fig. 1 Flow diagram of the study. In the original randomized controlled trial (RCT), patients were randomly allocated into two groups, with both initially receiving cyclosporine for 6 months to maintain a whole-blood trough level between 80 and 100 ng/ml. Over the next 18 months, the dose was adjusted to maintain a slightly lower (60–80 ng/ml) trough level in Group A (*regimen A*), while Group B received a fixed dose of 2.5 mg/kg/day, corresponding to a trough level of approximately 20–40 ng/ml (*regimen B*). Seven patients allocated to Group B received the regimen for Group A.

treatment in our previous RCT, 11 were excluded from analysis in that study due to protocol violation (10 patients) and ineligibility (1 patient). In the present follow-up analysis, however, all children who received the protocol treatment were eligible, and eight children (protocol violation in original study, 7; ineligibility, 1) were enrolled.

Basic characteristics of patients

Characteristics of the 46 participants of the present follow-up trial and nine children who were lost to follow-up are shown in Table 1, with exclusion of the one patient who withdrew immediately after entry. Of the 46 patients, 39 were male. Mean age (± SD) at onset of nephrotic syndrome and at the start of protocol treatment in the original RCT was 5.7 ± 3.9 and 8.7 ± 4.5 years, respectively.

Outcomes associated with relapse, immunosuppressants and risk factors

The median follow-up periods from onset of nephrotic syndrome and from the start of the treatment protocol was 12.3 [interquartile range (IQR) 10.4–14.2] and 10.3 (IQR 8.9–12.2) years, respectively. At last follow-up (mean age 18.7 ± 4.3 years), ten patients (21.7 %) were classified as being in disease-free remission, including one who had a history of SRNS; 23 (50.0 %) were categorized as FRNS/SDNS (6 patients) or with major immunosuppression (17 patients), taking cyclosporine (9), high-dose mizoribine (2) or both (6), to control the FRNS/SDNS; five (10.9 %) were categorized as minor immunosuppression (on regular-dose mizoribine); eight (17.4 %) were categorized as infrequent relapse (Fig. 2a). No notable differences in results were found when the analysis was restricted to patients aged ≥18 years at last observation (n=19, median follow-up period from onset 13.2 years; IQR 9.7–18.9 years; Fig. 2b).

During the follow-up period, two patients continued to receive cyclosporine, 25 were restarted on cyclosporine, 23 received mizoribine, an agent in the same antimetabolite class as mycophenolate, six received cyclophosphamide and two received steroid pulse therapy. The duration of cyclosporine administration after the treatment protocol varied widely, from 2.0 to 12.7 years, of which median duration was estimated to be 5.3 (95 % confidence interval 4.0–7.0) years by the Kaplan–Meier method. No patient received mycophenolate mofetil or rituximab during the follow-up period.

A proportional odds model did not identify any significant independent risk factor contributing to relapse upon stratification into three levels: (1) low, disease-free remission; (2) medium, infrequent relapse and minor immunosuppression; (3) severe, FRNS/SDNS and major immunosuppression (Table 2).

Time to disease-free remission from the start of the treatment protocol treatment and from the onset of nephrotic syndrome is shown as Kaplan–Meier plots in Fig. 3). Of note, patients who did develop remission tended to do so relatively early in the course of their disease. The mean age at the start of ongoing remission without any immunosuppressants was 11.5 ± 5.1 years.

Table 1 Background characteristics of the participants in the original randomized controlled study and present follow-up study

Background characteristics	Patients analyzed in the present follow-up study	Patients not followed-up	All patients	*p* value
All	46	9	55	
Sex				
Male	39	6	45	0.20
Female	7	3	10	
Age at onset (yr)	5.7 ± 3.9	7.2 ± 3.9	5.9 ± 3.9	0.29
Age at protocol treatment (yr)	8.7 ± 4.5	12.2 ± 3.8	9.3 ± 4.5	0.03
Cyclophosphamide before protocol treatment				
Yes	21	3	24	0.50
No	25	6	31	
Steroid dependency before protocol treatment				
Yes	31	5	36	0.33
No	12	4	16	
Unknown	3	0	3	
Height SD score during treatment protocol	−0.9 ± 1.2	−0.8 ± 1.7	−0.9 ± 1.3	0.96
BMI during treatment protocol (Kg/m^2)	20.9 ± 3.5	19.5 ± 4.0	20.6 ± 3.6	0.30
eGFR at protocol treatment (ml/min per 1.73 m^2)	142.6 ± 49.6	143.9 ± 30.7	142.8 ± 46.8	0.73
eGFR <90	4	0	4	1.00
eGFR ≥90	42	9	51	

BMI, Body mass index; eGFR, estimated glomerular filtration rate; SD, standard deviation

Data are presented as the number (of patients) or as the mean ± SD

Complications and adverse effects

Several complications and adverse effects were recorded at the last observation, most of which were likely due to steroid treatment (Table 3). No patient experienced SRNS or death during the follow-up period. The mean eGFR at last observation was 130.2 ± 25.3 ml/min per 1.73 m^2 (n=45), and no patient had an eGFR of <90 ml/min per 1.73 m^2. The mean SD score for height at the last observation was −0.79 ± 1.20, and six patients were below −2 SD (minimum −4.7 SD). Obesity was evaluated using the body mass index (BMI). Excess body weight (BMI>90th percentile of Japanese reference value; http://jspe.umin.jp/eng/index.html) was observed in seven patients, four of whom suffered from obesity (BMI> 97th percentile of Japanese reference value). Upon stratification by main outcome, all adverse effects were more frequent in the 23 (of 46) patients who were categorized with FRNS or major immunosuppression—significantly so for short stature and osteoporosis (both p=0.02) (Table 3).

Discussion

In this long-term follow-up study, we found that the majority of children with FRNS who received the treatment protocol of cyclosporine for 2 years continued to experience relapses of nephrotic syndrome approximately 10 years later. Nevertheless, the overall outcome in terms of survival and renal function was favorable. This study, to our knowledge the first long-term follow-up study of an RCT in a well-defined group of children with FRNS, confirms the long-term relapsing nature of FRNS beyond adolescence and into adulthood.

Of particular note, the rate of one or more relapses or use of immunosuppressants in our patients during the last 2 years of the observational period was high (78.3 %) compared to the rate of FRNS/SDNS or major immunosuppressant use for the control of relapse during this same period (50 %). This relapse rate is higher than those reported in three earlier studies [6–8]. However, while these latter three studies highlight the long-term relapsing nature of FRNS, each has methodological issues that preclude comparison with our results: (1) all were retrospective chart reviews of patients under treatment in general practice settings at single centers; (2) the patients were older than our patients at last observation; (3) outcome categorizations were not precisely classified; (4) two of the three studies were not restricted to FRNS but enrolled patients with SSNS [6, 7]. With regard to age, our results did not substantially change when the analysis was limited to patients aged≥18 years at last observation. Further, only 22.7 % of our patients achieved disease-free remission at 10 years from the start of the treatment protocol. These results indicate that