Cyclophosphamide and Rituximab in frequently relapsing/steroid-dependent nephrotic syndrome

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Abstract

Background

Steroid-sensitive nephrotic syndrome is the most common form of nephrotic syndrome in childhood, defined by the response to treatment with glucocorticoids with consequent remission. Whilst most children eventually experience spontaneous resolution of the disease, some have a difficult course with frequent relapses or steroid-dependence (FRSDNS). The consequent steroid toxicity often prompts administration of other immunosuppressive drugs, traditionally cyclophosphamide. Recently, rituximab has been reported as effective in this disorder, but long-term experience is lacking.

Methods

Retrospective note review of all children with FRSDNS treated with a first course of cyclophosphamide and/or rituximab in our centre between December 2006 and April 2015. We reviewed time to first relapse after treatment, co-medications and side effects.

Results

A total of 102 children were treated with cyclophosphamide (79) and/or rituximab (42). Of these, 34 received cyclophosphamide prior to rituximab. Median time to first relapse was 7 months after cyclophosphamide and 14 months after rituximab. Documented side effects of cyclophoshamide included neutropaenia, hair loss and haemorrhagic cystitis (1). Rituximab was associated with an allergic reaction at infusion in 2 patients.

Conclusion

Rituximab was used in children with the most difficult to treat FRSDNS, yet was associated with longer remission time and less side effects than cyclophosphamide. A randomized controlled trial is needed to directly compare these drugs.

Introduction

Idiopathic nephrotic syndrome is a rare disease in childhood with an estimated incidence of 16:100000 [1]. Most children have so-called steroid-sensitive nephrotic syndrome (SSNS), defined by the response of the disease to treatment with glucocorticoids, typically prednisolone. A kidney biopsy, which nowadays is rarely obtained, would typically show “minimal changes” on light microscopy and foot process effacement on electron microscopy. The aetiology is unclear, but thought to be immune-mediated, as “immune stimulators” such as infections and vaccines are classical triggers for the disease and because of the response to immunosuppressive medications. The spectrum of severity is wide, with some patients only suffering a single episode, whilst others have a chronic relapsing course with consequent toxicity from repeated or ongoing use of glucocorticoids, including obesity, striae distensae, stunted growth, behavioural abnormalities and osteoporosis. Fortunately, the disease resolves spontaneously in the majority of children, with less than 10% of patients having ongoing relapses into adulthood, although this proportion may be higher in FRSDNS [2]. Consequently, the main aim of the treating physician is to guide the individual patient safely through the active disease period with the least side effects. To minimise steroid toxicity, other immnosuppressive drugs are frequently used, also called “steroid-sparing medications”. These include cyclophosphamide, mycophenolate mofetil and calcineurin inhibitors [1].

Over the last years, case reports have emerged on the successful use of rituximab in FRSDNS, as well as some case series [3-6]. These reports demonstrate that rituximab is increasingly used in FRSDNS and a few recent randomised controlled

trials suggest a benefit of rituximab in minimising the use of steroids and other immunosuppressive drugs [8-11].

The nephrotic clinic at Great Ormond Street Hospital for Children (GOSH) is a referral clinic for children with difficult to treat nephrotic syndrome. Patients with SSNS are usually cared for by paediatricians in their local hospital, but get referred to GOSH, if they develop FRSDNS. The decision for and choice of steroid–sparing medications is made in conjunction with the family after discussion of the benefits and side effects of the individual drugs. In those with persistent relapses and/or unacceptable side effects despite one or more steroid-sparing drugs, we have increasingly used rituximab to achieve prolonged remission. However, long-term experience with the use of this drug in FRSDNS is still scarce and we thus reviewed data from our own centre to better inform treatment choice in children with FRSDNS.

Methods

We performed a retrospective review of notes from patients with SSNS, who received treatment with a first course of cyclophosphamide and/or rituximab. Patients were identified from a database maintained by the nephrotic service. We first used rituximab in FRSDNS in December 2006 and thus chose the time period for this review from this date to April 2014, to ensure a minimum of 1 year of follow-up. For comparison, we reviewed the notes of those patients who received a first course of cyclophosphamide during the same time period. We only included those patients, who received at least 50% of the prescribed dose of either rituximab or cyclophosphamide to ensure sufficient drug was given to expect a response.

We analysed time to first relapse after treatment with either of these drugs, as well as documented side effects and other immunosuppressive medications used.

In our clinical practice, a relapse is defined as 3 days of 3+ on dipstick for protein, plus presence of oedema and/or hypoalbuminaemia (<25g/l).

Time to relapse was compared and graphically illustrated using SPSS version 22.0 software. Mann-Whitney U test was used to assess significance in the comparison of median values.

Results

Patient cohort

A total of 104 children (70 male, 34 female) were identified who had been prescribed a first course of cyclophosphamide or rituximab during the stated period: 79 patients (53 male) had been prescribed cyclophosphamide (standard dose of either 2 mg/kg for 3 months or 3 mg/kg for 2 months) with a median age of 6 years (range 1-15 years) at the beginning of the course. All patients prescribed cyclophosphamide received at least 50% of the dose.

Forty-four patients (34 male) had been prescribed rituximab, either a single dose of 750mg/m2 (N=10), or 2 doses of 750 mg/m2 approximately 2 weeks apart (N=34). The infusion of rituximab had to be abandoned at the very beginning in 2 patients due to an allergic reaction. These 2 patients were not included in the analysis, as they did not receive sufficient dose to expect an effect.

Of the 42 patients who received rituximab, 35 (83%) had received a course of cyclophosphamide previously, including 20 who received it within the review period.

Baseline data for the patients are presented in table 1.

Time to first relapse

Median time to relapse was 7 months following cyclophosphamide treatment and 14 months following rituximab (see Figure 1).

Long-term remission (>24 months) was assessed in patients, who had at least 2 years of follow-up after treatment and was achieved in 24% after cyclophosphamide and 32% after rituximab.

Other immunosuppressive medications at commencement of cyclophosphamide or rituximab treatment

At the time of commencement of cyclophosphamide, all children received prednisolone, at a median dose of 0.4mg/kg/day.

37 patients receiving a first course of cyclophosphamide received levamisole prior to starting, which was stopped in all when starting cyclophosphamide. Two patients received treatment with a CNI, which was also stopped at commencement of cyclophosphamide. For the remaining 40 children cyclophosphamide was the first "steroid sparing" medication prescribed.

Of the 42 children receiving rituximab, 14 were treated with maintenance prednisolone only, 18 were treated with a calcineurin inhibitor (CNI) and prednisolone, 8 with mycophenolate mofetil (MMF) and prednisolone, and 2 with a combination of CNI + MMF + prednisolone. In total, 28 children (67%) received at least 2 other immunosuppressants including prednisolone at the time of rituximab administration. Median dose of Prednisolone at the time of the rituximab treatment was 0.3 mg/kg/d.

Immunosuppressive medications at first relapse after cyclophosphamide or rituximab treatment

Within the cyclophosphamide group 67 children (84%) were weaned off prednisolone with a median time to stop prednisolone of 3 months. Median time off prednisolone until 1st relapse was 3 months. 12 patients (16%) were still on maintenance prednisolone when they relapsed.

Within the rituximab group, 36 children (86%) were weaned off prednisolone with a median time to stop prednisolone of also 3 months. Six patients (14%) relapsed whilst still on prednisolone. Median time off prednisolone until 1st relapse was 12 months. In 29 children (69%) all immunosuppressive medications were weaned off within a median time of 4 months. Seven children weaned off prednisolone, but relapsed whilst still receiving a CNI or MMF.

Side effects

Side effects were not systematically documented in the notes, especially minor ones, such as hair loss and thus are difficult to compare. However, in 3 patients receiving cyclophosphamide there was documented neutropenia with consequent adjustment of the dose and/or premature stopping of the drug. One patient had to be hospitalised due to bladder obstruction from a clot from haemorrhagic cystitis and required surgical bladder washout by cystoscopy under general anaesthesia.

In the patients receiving a first course of rituximab, no specific side effects were noted, except for the allergic reaction in 2, which prevented further administration of the drug.

Patients who had received cyclophosphamide and rituximab

Of the 42 patients who received rituximab, 34 had previously also received cyclophosphamide, 19 within the review period. Time between the 2 treatments varied between 8 to 173 months. To assess the drug effect within the same cohort of children, we compared time to relapse for the 2 drugs in these 34 patients.

The median time to relapse after receiving cyclophosphamide was 2 months (range 0 to 29 months). The median time to relapse after receiving rituximab was 15 months (1-73 months, with 12 patients so far not having had a relapse).

We also assessed the median time to relapse after rituximab in those children who had previously received cyclophosphamide to those who did not. Median time to relapse in children with a previous cyclophosphamide course (N=34) was 16 months compared to 9 months in those without (N=8). This difference was not significantly different (P=0.305).

Rituximab dosing

Initially, all children treated with rituximab received 2 doses of 750 mg/m2, as adapted from our protocol for Systemic Lupus Erythematodes [12]. With reports emerging of single-dose treatment in FRSDNS, we changed the protocol to a single dose of 750 mg/m2. A total of 8 patients were treated with this single dose regime, but when 6 of these relapsed within 8 months, we reverted to the old two-dose protocol. The median time to relapse in the two-dose regimen (N=34) was 16 months (range 1-73), whereas it was 5 months (range 1-36) with a single dose, which was significantly different (p=0.03).

Discussion

This is a retrospective review of the response to cyclophosphamide and/or rituximab in children with FRSDNS. Thus, a direct comparison between the 2 drugs is possible only to a limited extent, as clinical circumstances were not controlled, especially with respect to medications received previously and during the course. Nevertheless, our data suggest that rituximab plays an important role in the treatment of FRSDNS with a median time to relapse of 14 months compared to 7 months after cyclophosphamide (Figure 1). The response to rituximab in our centre with regards to time to relapse is similar to that in other recent reports in children with FRSDNS of 6 -18 months [6, 9-11, 13]. The response to cyclophosphamide recorded here is also well within the range of reports in the literature [14] and is comparable to the efficacy of levamisole and MMF with a recently reported median relapse free interval of approximately 7-8 months [15].

A key aim of these so-called steroid-sparing agents is to minimise the use of glucocorticoids. Whilst the vast majority of children (84% after cyclophosphamide and 86% after rituximab) could come off prednisolone completely, this effect was much more sustained after rituximab, consistent with the prolonged remission: the median time off prednisolone after rituximab was 12 months, compared to only 3 months after cyclophosphamide.

Some of this apparent superior effect may have been simply due to the more intensive immunosuppression received concomitantly: at the start of the respective treatment courses, children receiving cyclophosphamide were only receiving prednisolone as additional immunosuppression, whereas the majority of patients

(67%) receiving rituximab received at least one additional immunosuppressant besides prednisolone, that is a CNI and/or MMF. However, this is not supported by the assessment of the number of immunosuppressants at the time of first relapse, as the majority (69%) of children could come off all immunosuppressants after rituximab. Indeed, rather than providing an alternative explanation for the prolonged remission after rituximab, the higher number of immunosuppressants at the beginning of treatment more likely reflects the severity of the disease: in our clinical practice at GOSH, treatment with rituximab has so far been reserved for patients with the most difficult to treat FRSDNS, who either continue to have relapses despite the use of one or more steroid sparing agents or experience side effects deemed unacceptable. In contrast, cyclophosphamide is typically the first steroid-sparing immunosuppressive drug used in children with FRSDNS referred to our clinic. Thus, rituximab was given only to a selected cohort with the most difficult to treat form of FRSDNS. We aimed to account for this potential selection bias by comparing the effect of the 2 drugs in those patients who had received both drugs. When analysing just those 34 patients, the superior response to rituximab is even more remarkable with a median time to relapse of 17 months compared to only 2.5 months after cyclophosphamide. It is, of course, also possible, that some patients with FRSDNS respond better to cyclophosphamide than to rituximab. The patients, who entered long-term remission after cyclophosphamide and never received rituximab could be examples for such superior cyclophosphamide responders. The superior effect of cyclophosphamide in these patients would not be captured in our study, as rituximab was given only to those patients who continued to have relapses with other treatments. Thus, the nature of this retrospective review may bias against

cyclophosphamide. Only a prospective study would be able to answer this question in an unbiased fashion.

The apparent superior efficacy of rituximab in FRSDNS appears not to be complicated by more severe side effects. Whilst not systematically documented, the only noted side effects were an allergic reaction to the drug during infusion. Nevertheless, severe complications have been reported after rituximab, most notably progressive multifocal encephalopathy from reactivated Jacob-Creutzfeld virus and progressive pulmonary fibrosis [16-18]. Fortunately, these severe complications appear to be exceedingly rare and since these patients received other concomitant immunosuppressive treatment, the precise contributing effect of rituximab is difficult to assess. Interestingly, in a trial of rituximab in lupus nephritis, the frequency of reported side effects was higher in the placebo than in the rituximab group [19].

Currently, no consensus exists about the optimal dosage of rituximab in FRSDNS with reported dosages ranging from 375 to 1500 mg/m2 divided into 1 to 4 injections [3]. In the original indication of lymphoma treatment, the dose of 1500 mg/m2 divided into 4 injections was developed and this dose has been adapted for subsequent indications, such as SLE [16]. However, in a few recent trials in FRSDNS, only a single injection of 375 mg/m2 has been used with apparent good effect [9, 11]. Whilst repeated dosing results in extended half-life [20], it is unclear whether this translates into clinical benefit. Evidence from some case series seems to suggest that repeated dosing may be associated with longer remission compared to single-dose treatment [21], which fits our experience here. Further studies are needed to identify the optimal dosage for this indication in children, but if equivalent a smaller drug dose or decreased frequency would obviously be preferable with respect to cost and potential side effects.

Conclusions

This retrospective review clearly supports the efficacy of rituximab in FRSDNS, which is superior to cyclophosphamide: time to first relapse and time off steroid post treatment was 2 and 4 times longer, respectively, after rituximab. Superiority was even more pronounced when just reviewing the most difficult to treat patients, that is those, who received both cyclophosphamide and rituximab during the course of their disease.

Our data raise the question, whether rituximab should continue to be reserved only for the most difficult to treat patients or whether it could be a superior first line steroid-sparing agent in patients with FRSDNS. Randomized, controlled clinical trials are needed to properly address this question.

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Table 1

	CycP only	Ritux only	CycP and Ritux
N	59	8	34
Male (%)	66	87	82
Median age at treatment (years)	6	7.5	11
Biopsy , N (%)	11 (19)	6 (75)	15 (44)
MCN, N (%)	9 (82)	5 (83)	11 (73)
FSGS, N (%)	2 (18)	1 (17)	4 (27)
Previous steroid sparing meds, N (%)	29 (49)	8 (100)	30 (88)
Levamisole, N (%)	28 (47)	2 (25)	18 (53)
CNI, N (%)	1 (2)	8 (100)	25 (74)
MMF, N (%)	1 (2)	5 (63)	9 (26)

Table 1: Baseline data of patients

Numbers for previous steroid sparing medications do not necessarily add up, as some patients received more than one such medication prior to cyclophosphamide (CyCP) or Rituximab (Ritux). Median age at treatment in the group receiving both CyCP and Ritux refers to age at Ritux treatment. Similarly, for the same group, previous steroid sparing medications refer to medications prior to Ritux treatment. CNI: Calcineurin inhibitor, MMF: Mycophenolate Mofetil

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Figure 1

Kaplan-Meyer graph of time to first relapse in children having received a first course of rituximab (blue line, N=42) or cyclophosphamide (red line, N=79). Median time to first relapse was 14 months after rituximab and 7 months after cyclophosphamide.