Refractory mixed proliferative and membranous lupus nephritis treated with the topoisomerase I inhibitor irinotecan as add-on therapy

R Biesen[1], M Frese-Schaper[2], P Enghard[3], Q Cheng[2], F Hiepe[1,2], S Frese[2,4]

[1]Department of Rheumatology and Clinical Immunology, Charité Universitätsmedizin Berlin, Berlin, Germany
[2]Deutsches Rheuma-Forschungszentrum Berlin (DRFZ), a Leibniz Institute, Berlin, Germany
[3]Department of Nephrology and Intensive Care Medicine, Charité Universitätsmedizin Berlin, Berlin, Germany
[4]Department of Thoracic Surgery, Lungenklinik Lostau, Lostau, Germany

Objective: To evaluate the safety and effects of irinotecan, an inhibitor of topoisomerase I, on refractory lupus nephritis.
Method: A patient with refractory lupus nephritis under medication with mycophenolic acid, prednisolone, and hydroxychloroquine was treated with add-on low-dose irinotecan. Irinotecan was applied every fourth week at a dose of 50 mg/m^2 for four cycles followed by 100 mg/m^2 for another eight cycles. Renal function and anti-double-stranded DNA antibodies as well as blood count for evaluation of side effects were assessed during the treatment with irinotecan.
Results: Before starting the treatment with irinotecan, a urine protein/creatinine ratio of 1298 mg/g was determined. This declined to 613 mg/g after four cycles with 50 mg/m^2 irinotecan and was further reduced to 198 mg/g when using the higher dose of irinotecan. Kidney function remained stable, with creatinine levels of 1.66 mg/dL at the beginning and 1.76 mg/dL at the end of treatment with irinotecan. Importantly, no side effects, such as diarrhoea or neutropenia, were observed during the entire course of treatment.
Conclusion: Administration of low-dose irinotecan as add-on medication for the treatment of refractory lupus nephritis was shown to be safe. Clinical trials are needed to determine whether irinotecan can improve kidney function and the outcome of patients with refractory lupus nephritis.

Refractory lupus nephritis has been defined by the European League Against Rheumatism for patients under immunosuppressive therapy who do not achieve a partial response within 6–12 months (1). Despite intensive treatment, the disease may lead to life-threatening organ damage and, therefore, represents an unmet medical need (2). In 2010, our group found by serendipity that the topoisomerase I inhibitor irinotecan suppressed murine lupus nephritis (3). While irinotecan at high doses has been used for many years to treat metastatic colorectal cancer (4), the doses needed to reverse advanced lupus nephritis in mice were more than 50 times lower (5). Importantly, treatment of lupus-prone mice with irinotecan did not induce profound immunosuppression (3, 5–7). Further studies indicated that topoisomerase I and its inhibitor modified double-stranded DNA (dsDNA) and subsequently binding of anti-dsDNA antibodies (5–7). Since topoisomerase I is phylogenetically highly preserved (8) and because irinotecan suppressed lupus nephritis in both NZB/NZW and MRL/*lpr* mice (7), we hypothesized that low-dose irinotecan could be a potential new treatment for lupus nephritis, using DNA modification rather than immunosuppression as a mechanism (9). In 2021, the beneficial effects of topoisomerase I inhibition on murine lupus nephritis were proven in an independent study using low-dose camptothecin and topotecan (10).

Case report

We report the case of a 59-year-old female patient presenting for the first time in 2013 with arthralgia, arthritis, alopecia, and Raynaud's syndrome, yielding the diagnosis of systemic lupus erythematosus with secondary Sjögren's syndrome. From November 2013, methotrexate and hydroxychloroquine were given for 5 months. Hydroxychloroquine was discontinued because of intolerance. After developing proteinuria, renal biopsy was performed in April 2014 which showed class III glomerulonephritis in combination with class V. From April 2014 to May 2015, 12 cycles of cyclophosphamide were applied, followed by administration of mycophenolate mofetil for 3 months, followed by azathioprine until February 2017. A second renal biopsy was undertaken in February 2017, demonstrating class IV glomerulonephritis in combination

Steffen Frese, Lungenklinik Lostau, Lindenstrasse 2, Lostau D-39291, Germany.
E-mail: steffen.frese@email.de

Accepted 13 September 2021

DOI: https://doi.org/10.1080/03009742.2021.1980979

with class V. From February 2017 to September 2017, another six cycles of cyclophosphamide were given with a cumulative dose of 22 g. Since renal function and proteinuria further deteriorated while a high titre of anti-dsDNA antibodies was present, mycophenolate mofetil 2 g/day was reintroduced in October 2017, which was replaced by mycophenolic acid 720 mg/day owing to constipation. The concomitant prednisolone dose varied between 5 and 10 mg/day. Until now the patient has also received quintuple antihypertensive therapy, including an angiotensin-converting inhibitor.

In June 2018, lupus nephritis was classified as refractory to treatment with mycophenolic acid and prednisolone, showing high proteinuria and serum creatinine (Figure 1A, B) and increased blood pressure. Because the patient had a vacation planned, a high-dose prednisolone treatment course was initiated, followed by the first irinotecan application in August 2018, after obtaining informed consent from the patient. Irinotecan was administered i.v. at a dose of 50 mg/m^2 in an outpatient setting as add-on therapy to mycophenolic acid, prednisolone (5–10 mg/day), and newly started hydroxychloroquine. Treatment with irinotecan was repeated every fourth week. The cumulative dose of irinotecan administered in this way was 9.3 times lower than the dose used for chemotherapy (4). The treatment protocol was approved by the internal review board of the hospital. The patient's consent for publication was obtained.

Although the urine protein/creatinine ratio declined from 1298 mg/g to 613 mg/g, no improvement in renal function was seen after four cycles of irinotecan (Figure 1A, B). Therefore, the dose was escalated to 100 mg/m^2. Ten days after the fifth application, an unexpected peak in the urine protein/creatinine ratio was observed, followed by a notable

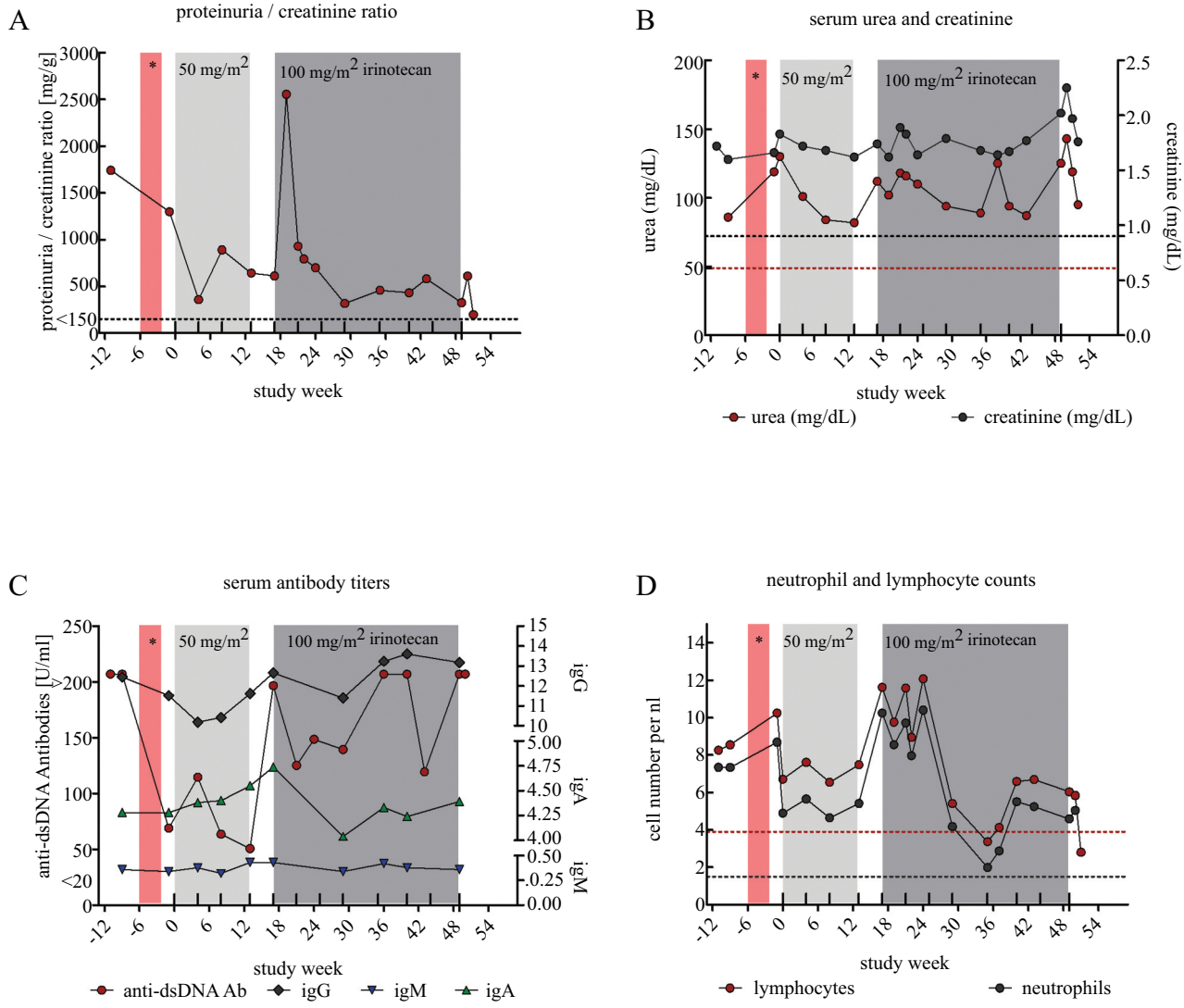

Figure 1. Changes in (A) urine proteinuria/creatinine ratio, (B) serum urea and serum creatinine, (C) levels of serum antibodies, and (D) neutrophil and lymphocyte counts were monitored during the course of add-on treatment with the topoisomerase I inhibitor irinotecan. *High-dose prednisolone treatment course. Dotted lines represent the normal range for the respective values. anti-dsDNA, anti-double-stranded DNA; Ig, immunoglobulin.

decline to 198 mg/g (Figure 1A). During the entire course of irinotecan treatment, with a total of 12 cycles (four cycles using 50 mg/m^2 and eight cycles using 100 mg/m^2), kidney function did not improve but remained stable (Figure 1B); the lack of amelioration was probably caused by the long history of kidney involvement with irreversible damage. Remarkably, no adverse effects of irinotecan, such as diarrhoea or a reversible neutropenia of short duration (4), were seen (Figure 1D). Furthermore, there was no evidence of a marked additional immunosuppression caused by low-dose irinotecan: neutrophil and lymphocyte counts were within normal ranges, immunoglobulin (IgG, IgM, and IgA) serum concentrations remained normal, and anti-dsDNA antibody titres were stable (Figure 1C). Complement (C3 and C4) showed normal levels at the beginning of irinotecan treatment and stayed normal during treatment with the lower irinotecan dose. There was some decrease in complement when using the higher dose of irinotecan, with a C3 level of 39 mg/dL and a C4 level of 6 mg/dL at the end of the treatment course. Most importantly, we did not observe any relevant infections.

Discussion

More than a decade after the initial finding of beneficial effects of the topoisomerase I inhibitor irinotecan on murine lupus nephritis, which was made by serendipity by a medical doctor not working in the field of rheumatology/nephrology (3), we report here the first patient with refractory lupus nephritis treated with low-dose irinotecan. Despite the fact that in mice extremely low doses of irinotecan were sufficient to treat advanced lupus nephritis (5), so far the rheumatological community has not started clinical trials. In line with that, it took a decade until an independent research group proved the concept of topoisomerase I inhibition for the treatment of at least murine lupus nephritis (10). However, there are arguments for the use of topoisomerase I inhibitors in the treatment of human lupus nephritis. First, the topoisomerase I inhibitor irinotecan was only needed in very low concentrations in mice to treat lupus nephritis (5, 6). Secondly, suppression of lupus nephritis by the topoisomerase I inhibitor worked in two independent mouse strains of lupus-like disease (3, 5, 7). Thirdly, suppression of lupus nephritis in mice was not accompanied by immunosuppression but may involve modification of dsDNA, resulting in an impaired binding of anti-dsDNA antibodies (5, 6). Fourthly, the enzyme topoisomerase I is phylogenetically highly conserved, showing 96% homology between mice and humans (8).

This is the first case reporting the use of the topoisomerase I inhibitor irinotecan for the treatment of systemic lupus erythematosus. The patient chosen for this treatment was probably not ideal owing to her long history of lupus nephritis with glomerulosclerosis and interstitial fibrosis lesions. Consequently, although a decline in urine protein/creatinine ratio was measured, no improvement in kidney function was seen, thus missing the criteria for a complete or partial response of lupus nephritis (11). The beneficial effect on the urine protein/creatinine ratio seen during the treatment period, however, may be related at least in part to the drug hydroxychloroquine, which was restarted at the same time as irinotecan. Most importantly, no adverse events in terms of additional immunosuppression, other than caused by the conventional medication used, were seen. Further clinical trials should recruit patients with refractory class III/IV lupus nephritis to determine whether irinotecan is able to reverse proteinuria and to improve kidney function.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the Deutsche Forschungsgemeinschaft [grant no. 317392477] to SF and by the non-profit organization LUNIRI (www.luniri.com) .

Author contributions

SF designed the study. RB and FH performed all consultations and treatments. MFS, PE, and QC performed analyses and collected data. MFS and SF wrote the first draft of the manuscript. All authors approved the final manuscript before submission.

References

1. Gordon C, Jayne D, Pusey C, Adu D, Amoura Z, Aringer M, et al. European consensus statement on the terminology used in the management of lupus glomerulonephritis. Lupus 2009;18:257–63.
2. Kronbichler A, Brezina B, Gauckler P, Quintana LF, Jayne DRW. Refractory lupus nephritis: when, why and how to treat. Autoimmun Rev 2019;18:510–8.
3. Frese-Schaper M, Zbaeren J, Gugger M, Monestier M, Frese S. Reversal of established lupus nephritis and prolonged survival of New Zealand black x New Zealand white mice treated with the topoisomerase I inhibitor irinotecan. J Immunol 2010;184:2175–82.
4. Vanhoefer U, Harstrick A, Achterrath W, Cao S, Seeber S, Rustum YM. Irinotecan in the treatment of colorectal cancer: clinical overview. J Clinical Oncol 2001;19:1501–18.
5. Frese-Schaper M, Keil A, Steiner SK, Gugger M, Korner M, Kocher GJ, et al. Low-dose irinotecan improves advanced lupus nephritis in mice potentially by changing DNA relaxation and anti-double-stranded DNA binding. Arthritis Rheumatol 2014;66:2259–69.
6. Keil A, Frese-Schaper M, Steiner SK, Korner M, Schmid RA, Frese S. The topoisomerase i inhibitor irinotecan and the tyrosyl-DNA phosphodiesterase 1 inhibitor furamidine synergistically suppress murine lupus nephritis. Arthritis Rheumatol 2015;67:1858–67.
7. Keil A, Hall SR, Korner M, Herrmann M, Schmid RA, Frese S. Suppression of lupus nephritis and skin lesions in MRL/lpr mice by administration of the topoisomerase I inhibitor irinotecan. Arthritis Res Ther 2016;18:243.

8. Koiwai O, Yasui Y, Sakai Y, Watanabe T, Ishii K, Yanagihara S, et al. Cloning of the mouse cDNA encoding DNA topoisomerase I and chromosomal location of the gene. Gene 1993;125:211–6.
9. Frese S, Diamond B. Structural modification of DNA – a therapeutic option in SLE? Nat Rev Rheumatol 2011;7:733–8.
10. Wang X, Oates JC, Helke KL, Gilkeson GS, Zhang XK. Camptothecin and topotecan, inhibitors of transcription factor Fli-1 and topoisomerase, markedly ameliorate lupus nephritis in NZBWF1 mice and reduce the production of inflammatory mediators in human renal cells. Arthritis Rheumatol 2021;73:1478–88.
11. Rovin BH, Furie R, Latinis K, Looney RJ, Fervenza FC, Sanchez-Guerrero J, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis Rheum 2012;64:1215–26.