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### Doxycycline for haematopoietic stem cell transplantation-related thrombotic microangiopathy

Transplantation-associated thrombotic microangiopathy (TA-TMA) is a devastating consequence of allogeneic haematopoietic stem cell transplantation (HSCT) with a mortality rate of 60–90%. None of the interventions used, as used up till now in idiopathic thrombotic thrombocytopenic purpura (TTP) (fresh frozen plasma transfusion, plasma exchange and steroids), were effective to treat TA-TMA [1,2]. We report a dramatic improvement of TA-TMA in two HSCT patients [conditioning, cyclophosphamide, total body irradiation, graft-versus-host disease (GVHD) prophylaxis] using doxycycline.

A 36-year-old woman with Hodgkin's lymphoma received an allogeneic HSCT in December 2002. Twelve months later, she developed a biopsy-proven TMA (proteinuria, 3 g/day, microscopic haematuria, oliguric acute renal failure with creatinine level at 680 µmol/L; haemoglobin Hb, 6.3 g/dL; schistocytes; platelet count,  $35 \times 10^9/L$ ; LDH, 1754 IU/L). The serum complement proteins were at normal levels, no mutations of the membrane cofactor protein were found and a plasma ADAMTS13 activity was found at 40%. Steroids, plasma exchange, fresh frozen plasma transfusion, vincristine and haemodialysis were tried with a partial response (haemoglobin, 7.3 g/dL, platelet  $70\,000/mm^3$  both after treatment). Doxycycline 200 mg daily was added for a suspected gastrointestinal *Bartonella* infection. Within two months, haemoglobin and platelet count rose without transfusion to 10.8 g/dL and  $234\,000/mm^3$ , respectively. Despite improvement of haematological parameters, the patient remained dialysis-dependent. The second patient had a similar haematologic disease and course under doxycycline prescribed for a Bartholinitis.

Five patients with TTP and *Bartonella*-like erythrocyte inclusions, successfully treated with doxycycline, experienced recurrence of their TTP following cessation of treatment [3]. TA-TMA has a multi-factorial aetiology of endothelial damage. Doxycycline targeting the adherens junction on endothelial cells prevents vascular hyperpermeability [4]. Doxycycline as a potential treatment of TA-TMA warrants further studies.

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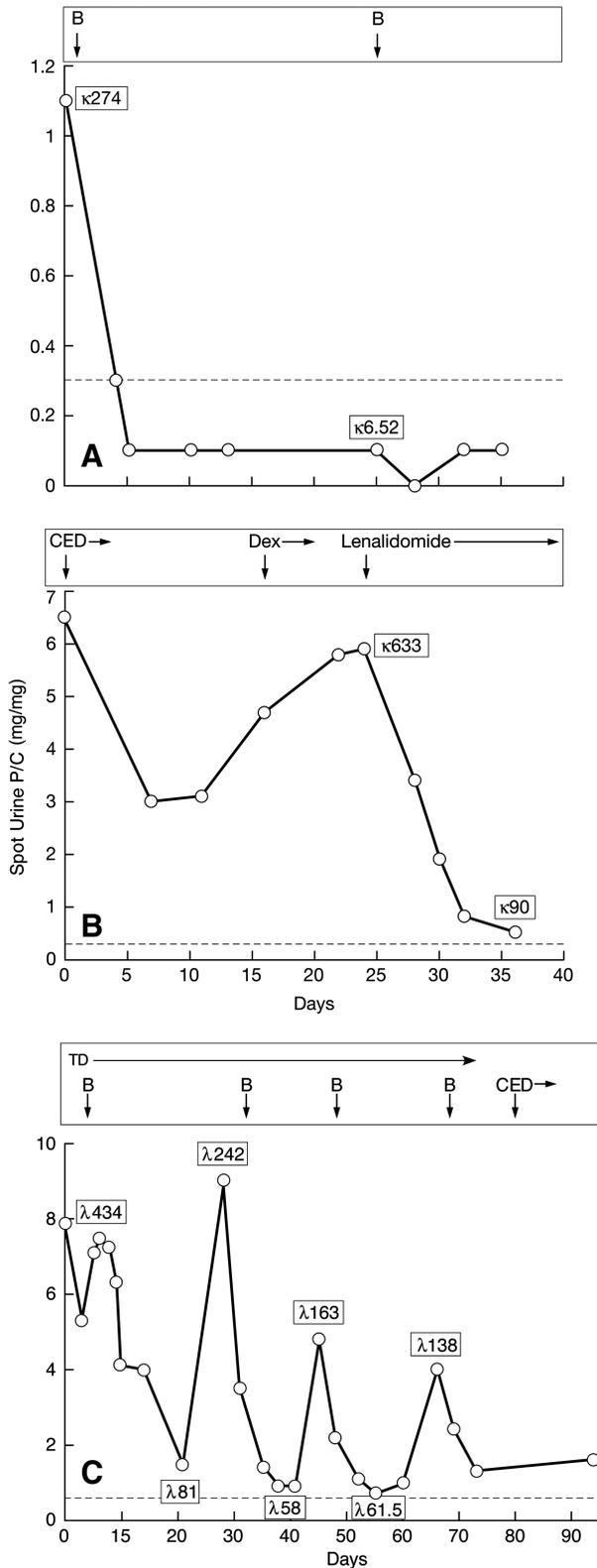
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### The spot urine protein/creatinine ratio is a simple, rapid and inexpensive method for monitoring patients with light-chain multiple myeloma

Protein electrophoresis of a 24-h urine collection (UPEP) is considered the standard method for following up patients with light-chain multiple myeloma [1]. The serum-free light-chain assay (SFLCA) has increasingly been used in this population [2], and in individual patients tracks well with proteinuria [3]. In addition, the SFLCA is also generally more sensitive than urine studies including immunofixation electrophoresis for detecting minimum residual light-chain disease [4,5]. However, the SFLCA is expensive, and due to inter-patient variation in the renal metabolism of light chains, the amount of proteinuria cannot be predicted by the SFLC concentration [1,5–7]. As proteinuria correlates better with renal dysfunction than SFLC and may be caused by factors other than light chains, serial measurement of urinary proteinuria is still considered essential [7].

The spot urine protein/creatinine ratio (SUPCR) has increasingly replaced the 24-h urine in patients with proteinuria from a variety of causes [8], but has not been examined in patients with multiple myeloma. As free light chains have a half-life of 2–6 h [9], the SUPCR is theoretically ideally suited to measure response to treatment within days of beginning therapy, and moreover, can be inexpensively and serially measured with rapidly available results. In this report, five patients with predominantly light-chain multiple myeloma were followed up by SUPCR and SFLCA. In Patient 1 and 2 (Figure 1A and B), progressive disease and subsequent response to therapy were accurately detected by SUPCR and in agreement with changes in the SFLCA. In Patient 3 (Figure 1C), bortezom-



**Fig. 1.** Spot urine protein/creatinine ratio and involved serum-free light chain (FLC) in response to therapy. **(A)** Patient 1: Because of worsening proteinuria and renal insufficiency (creatinine 2.5 mg/dL), bortezomib was started followed by a rapid decrease in proteinuria and κ FLC. **(B)** Patient 2: After a brief decrease in proteinuria after cyclophosphamide/etoposide/dexamethasone chemotherapy, there was disease progression with no response to pulse dexamethasone followed by a sharp decrease in proteinuria and κ FLC after starting lenalidomide. **(C)** Patient 3: After bortezomib was added to thalidomide/dexamethasone, there was a decrease in proteinuria and λ FLC followed by a rebound after each 10-day rest period. Bortezomib (B) was given as four doses on Day 1, 4, 8 and 11 of each 21-day cycle. Spot urine protein/creatinine is reported as milligram per milligram. Serum-free light chains are reported as milligram per decilitre. Upper limit of normal for κ FLC is 1.94 mg/dL, and for λ FLC is 2.63 mg/dL. The dotted line on the x-axis represents the upper limit of normal (<0.3 mg/mg) of the spot urine protein/creatinine ratio.

mib was added to thalidomide and dexamethasone because of worsening renal insufficiency. Serial SUPCR demonstrated that the proteinuria decreased after each cycle of bortezomib followed by a rebound during each 10-day rest period. The changes in the SUPCR grossly paralleled changes in SFLC levels. A bone marrow examination showed extensive replacement by multiple myeloma, confirming treatment resistance.

Patient 4 had three consecutive SFLCA in which the free kappa light-chain levels were mildly increased, ranging from 14.2 to 15.3 mg/dL (nl <1.94 mg/dL). During this same interval, two SUPCR samples were dramatically elevated at 5.2 and 6.0 mg/mg (nl <0.3 mg/mg). UPEP of the spot urine sample showed that 79% of the proteinuria was monoclonal. As the monoclonal proteinuria was disproportionately higher than the mildly abnormal SFLCA results, the SFLCA was repeated utilizing higher dilutions, and the correct SFLC concentration was found to be ~10-fold higher. The falsely low results were attributed to 'antigen excess' [10].

Patient 5 was referred with lambda light-chain myeloma and deteriorating performance status. At her first visit, the free lambda light chain was 90 mg/dL (nl <2.63 mg/dL), but the SUPCR was markedly increased at 5.7 mg/mg. UPEP of the spot urine showed that most of the protein was albumin indicative of a glomerular lesion. A skin biopsy showed amyloid.

These preliminary results suggest that the SUPCR can be used to monitor response in patients with light-chain proteinuria and, in contrast to SFLCA, may detect other causes of proteinuria that can be further evaluated by electrophoresis. The SUPCR can also identify patients in whom the SFLCA is falsely low due to antigen excess.

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### Additional antibody suppression from rituximab added to conventional therapy in severe, refractory anti-GBM nephritis

Sir,

Anti-glomerular basement membrane (GBM) nephritis is an autoimmune disease characterized by IgG antibody-formation against the  $\alpha 3$  (IV)NCI non-collagenous region of type IV collagen resulting in rapid progressive glomerulonephritis and, ultimately, renal failure when left untreated [1]. Several novel agents have been used when conventional therapy fails to suppress antibody formation. We describe the case of a young woman with severe anti-GBM disease who had persistently high antibody titres despite conventional therapy, experiencing successful antibody suppression after rituximab was added to her therapeutic regimen.

A 20-year-old woman presented at the emergency department with acute, oliguric renal failure due to glomerulonephritis. Creatinine level was 624 mmol/L, urea level was 16 mmol/L, and 24-h protein excretion was 6.2 g. Anti-GBM titre was positive with 270 units, while ANCA-P3/MPO and ANA were negative.

The diagnosis of anti-GBM glomerulonephritis was made, and plasmapheresis was initiated while the patient was started on methylprednisolone 1 g i.v. for 3 days followed by 1 mg/kg and cyclophosphamide 2 mg/kg, both orally.

At Day 21, after 17 sessions of plasmapheresis with 3 L plasma volumes, the anti-GBM titre remained elevated at 180 units, and proteinuria worsened to 40 g/day.

Rituximab was initiated at a dose of 375 mg/m<sup>2</sup> with a 2-week interval. Four days after first rituximab treatment, the anti-GBM titre dropped to 130 units, and 11 days later the titre had further decreased to 85 units. Four weeks after the first dose of rituximab and 2 months after the diagnosis was made, the anti-GBM titre had dropped to below reference level, while proteinuria declined to 2 g/24 h and creatinine clearance rose to 32 (Modification of Diet in Renal Disease formula). Phenotyping of peripheral lymphocytes showed B cells to be almost completely absent.

The use of rituximab in anti-GBM nephritis has only been described in case studies, with mixed outcome, but its use has been successfully studied as adjuvant or salvage