Case Report

Successful treatment of multi-resistant *Pseudomonas aeruginosa* osteomyelitis after allogeneic bone marrow transplantation with a combination of colistin and tigecycline

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A case of osteomyelitis caused by multidrug-resistant *Pseudomonas aeruginosa* is reported in a patient who underwent allogeneic bone marrow transplantation for acute lymphoblastic leukaemia. The patient was successfully treated by prolonged administration of a full dose of colistin and tigecycline, and surgical curettage with the positioning of resorbable calcium sulfate pellets loaded with colistin.

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Introduction

Gram-negative bacteria remain a threat for neutropenic patients, such as recipients of high-dose chemotherapy or haematopoietic stem cell transplantation, especially when the organism is resistant to multiple antibiotics. Sepsis caused by multidrug-resistant *Pseudomonas aeruginosa* (MRPA) and the development of secondary haematogenous osteomyelitis is a rare complication that is often difficult to diagnose and treat. Therapeutic options are few if MRPA is susceptible *in vitro* only to polymyxin B, leading to mortality rates of between 18 and 61 % (Chatzinikolaou *et al.*, 2000; Jones *et al.*, 2004), amputation in 15 % of cases and recurrent infection in 60 % (Tice *et al.*, 2003). Based on *in vitro* studies, possible therapeutic strategies against MRPA include antibiotic combination therapy providing a synergistic effect, and the development of new antibiotic drugs (Rahal, 2006; Timurkaynak *et al.*, 2006). Tigecycline is a new broad-spectrum injectable antibacterial agent, the first member of a new class of antimicrobials, the glycylcyclines, derived from minocycline (Doan *et al.*, 2006). Despite a generally good efficacy against members of the family *Enterobacteriaceae*, tigecycline is not recommended alone for the treatment of infections caused by *P.*

aeruginosa because of the low prevalence of sensitive strains in *in vitro* studies (Doan *et al.*, 2006). Tigecycline does not appear to have reliable activity against *P. aeruginosa*, with an *in vitro* activity against the bacteria from 0.12 and 32 pg ml⁻¹ and with only 6.7 % of isolates inhibited by tigecycline at a concentration of <2 pg ml⁻¹ (Sader *et al.*, 2005a, b; Townsend *et al.*, 2006).

We used a combination of tigecycline and colistin because of the synergistic properties of these compounds against MRPA.

Case report

A 22-year-old white woman underwent allogeneic bone marrow transplantation (BMT) from a fully HLA-identical unrelated donor for acute lymphoblastic leukaemia in first complete remission. The conditioning regimen included intravenous (i.v.) busulfan (12.8 mg kg⁻¹, total dose), cyclophosphamide (120 mg kg⁻¹ i.v., total dose) and anti-thymocyte globulin (ATG Fresenius, 15 mg kg⁻¹ i.v., total dose). She received cyclosporin A and a short course of methotrexate (on days +1, +3 and +6) as graft-versus-host disease prophylaxis. In July 2006, 3 months before the BMT, the patient developed pneumonia due to fluoroquinolone-resistant *P. aeruginosa* (culture from bronchoalveolar lavage), which had been successfully treated with

Abbreviations: BCs, blood cultures; BMT, bone marrow transplantation; MRI, magnetic resonance imaging; MRPA, multidrug-resistant *Pseudomonas aeruginosa*.

piperacillin/tazobactam (13.5 g daily administered in continuous intravenous infusion) for a total of 20 days. At the time of the BMT (October 2006), the pneumonia had resolved, leaving a large ($6 \times 6 \times 6.5$ cm) sterile cavity in the right lung. A few days after the beginning of the conditioning regimen, the patient was already severely neutropenic (neutrophil count $<0.1 \times 10^3 \mu\text{l}^{-1}$). Considering the high risk of recurrence of *P. aeruginosa* infection, subcutaneous daily injections ($5 \mu\text{g kg}^{-1}$ daily) of granulocyte colony-stimulating factor were started. In addition, secondary antibiotic prophylaxis with piperacillin/tazobactam was initiated to minimize the risk of further infections caused by *P. aeruginosa*. By the sixth day after the transplant, the patient became febrile (Fig. 1) and blood cultures (BCs) showed growth of strains of *P. aeruginosa* sensitive to ceftazidime, imipenem and colistin. The prophylaxis regimen was stopped, and we started the administration of a third-generation cephalosporin (ceftazidime 2 g, three times daily) and amikacin (15 mg kg^{-1} daily). The patient did not develop cough or dyspnoea or other signs or symptoms suggestive of pneumonia. No signs of pulmonary parenchymal infection were demonstrated at the onset of the febrile episode on either standard

chest X-ray or lung high-resolution computerized tomography. Some days after the onset of the fever, she developed pain and swelling in the proximal part of the left leg, which appeared oedematous and warm. X-ray of the left tibia failed to show clear signs of bone involvement. Further BCs taken at days 10 and 14 after the transplant showed that MRPA was rapidly developing resistance to cephalosporins, aminoglycosides and carbapenems with sensitivity only to polymyxin B. According to the antibiogram, colistin was administered from day 16 after the BMT (4 million IU daily i.v.) combined with carbapenems (imipenem/cilastatin 2 g daily, and then meropenem 1 g three times per day). This drug combination was administered for 2 weeks.

With the recovery of the polymorphonucleated neutrophil (PMN) count on day +17 after the BMT, the clinical signs of sepsis improved with defervescence (Fig. 1), but local symptoms of osteomyelitis remained unmodified. From the recovery of PMNs, magnetic resonance imaging (MRI) (on day 32) (Fig. 2a), scintigraphy with radio-labelled autologous white blood cells (on day 33), and a bone biopsy (on day 39) confirmed the diagnosis of osteomyelitis due to the

Fig. 1. Trend of change in body temperature in °C during the febrile episode and treatment. (a) Ceftazidime 6 g daily plus amikacin 15 mg kg^{-1} daily; (b) switch to colistin 4 million IU daily; (c) addition of tigecycline 100 mg as loading dose, followed by 50 mg twice per day; (d) piperacillin/tazobactam 13.5 g daily plus amikacin 15 mg kg^{-1} daily. Pip/Taz, piperacillin/tazobactam; Cefta, ceftazidime; Amik, amikacin. (1) BCs, *P. aeruginosa* sensitive to ceftazidime, imipenem and colistin. (2) BCs, *P. aeruginosa* sensitive to imipenem and colistin. (3) BCs, *P. aeruginosa* sensitive to colistin. (4) BCs, negative. (5) BCs, negative. (6) Bone culture, *P. aeruginosa* sensitive to imipenem and colistin. (7) Necrotic material culture, *P. aeruginosa* sensitive to imipenem, piperacillin/tazobactam, amikacin and aztreonam.

Fig. 2. MRI of the proximal tibia showing bilateral osteonecrosis and soft tissue involvement in the left tibia related to infection (a) and MRI after treatment with combined antibiotic therapy and surgical curettage (b). (c, d) Plain X-ray of the proximal left tibia before (c) and after (d) curettage. Alteration of the tibial cortex is present preoperatively; after surgery, the curetted cavity was filled with colistin added to resorbable calcium sulfate pellets.

same strain of MRPA as cultured from the necrotic material and from the bone fragment. During this time, aminoglycosides (from days 28 to 34) and rifampicin (from days 28 to 42) were subsequently added to colistin. The *Pseudomonas* strain obtained from the previous BCs was tested against a large panel of antibiotics, and was sensitive only to colistin and to tigecycline ($\text{MIC} < 2 \text{ pg ml}^{-1}$). Initially, while we were waiting for the arrival of the tigecycline (kindly provided by Wyeth–Lederle for compassionate use), we added minocycline (from days 36 to 45) to the combination therapy. Tigecycline, 100 mg as a loading dose, followed by 50 mg twice daily, was added on day 46 to colistin based on the presumed synergistic effect of combination therapy and pursuing a more aggressive therapeutic approach on the soft tissues, and this therapy was administered for 12 days (colistin was administered for a total of 42 days). Tigecycline was given alone for another week (from days 58 to 65). After a few days of this combination therapy, the fever disappeared, as shown in Fig. 1, and the pain and tenderness of the tibial bone progressively decreased and disappeared on the sixth day. However, because of the high risk of recurrence of the osteomyelitis, surgical curettage of the left proximal tibia was performed 62 days after the transplant and resorbable calcium sulfate pellets coated with colistin were placed in the bone cavity to permit prolonged local release of the antibiotic (Fig. 2d) (Nelson *et al.*, 2002). Swabs were taken during surgery and the presence of the same strain of MRPA was confirmed. After surgery, combined antibiotic therapy with piperacillin/tazobactam plus amikacin was continued for a further 14 days, to complete the 9 week scheduled programme of antibiotic therapy (Fig. 1).

Three weeks after curettage, MRI showed reduced extension of the osteonecrosis and decreased inflammation of the surrounding tissues (Fig. 2b).

At 8 months after the BMT, the patient is in complete remission of her haematological malignancy, does not show any clinical sign or symptom related to the osteomyelitis and a further MRI scan taken at 8 months showed a resolution of the osteomyelitis.

Discussion

Serious infections are frequent complications of unrelated donor BMT, and nonrelapse mortality due to infections has an incidence ranging from 45 to 60 % in the first year after the transplant (Williamson *et al.*, 1999; Parody *et al.*, 2006). *P. aeruginosa* is considered an emerging and re-emerging issue in immunocompromised subjects, such as those who undergo BMT. In this subset of patients, the infections caused by MRPA represent a potentially life-threatening complication, usually requiring combined antibiotic therapy, sometimes leading to serious toxicity (such as following systemic colistin administration), and can be considered a marker for a poorer outcome.

After BMT, osteomyelitis appears to have a poor prognosis, but it is not a frequent complication. Furthermore, *P. aeruginosa* can rapidly disclose a multidrug-resistant profile, making the management of the infection increasingly difficult (Tice *et al.*, 2003). As in this case, a single agent often represents the only therapeutic option available, with the consequent risk of a suboptimal treatment of the infection. However, it is widely accepted that the synergistic effect of two or more antibiotics has significantly better results than their efficacy as single agents.

In animal models, tigecycline has displayed good bone penetration and therapeutic levels of the drug have been found in infected and uninfected bones (Yin *et al.*, 2005).

In our case, the severity of the infection and the deeply immunocompromised status of the patient led us to evaluate the *in vitro* sensitivity of the cultured strain of MRPA to alternative drugs, although some of them, like tigecycline, had been reported to be poorly effective (Sader *et al.*, 2005a, b; Townsend *et al.*, 2006). This approach allowed the identification of an uncommon strain of MRPA sensitive to tigecycline, leading to the co-administration of tigecycline with colistin.

Previous studies have demonstrated that the most common adverse effects related to the administration of tigecycline are nausea and vomiting in approximately 30 and 20 % of patients, respectively (Townsend *et al.*, 2006; Ellis-Grosse *et al.*, 2005; Babinchak *et al.*, 2005), and they are also the most frequent cause of its discontinuation (Townsend *et al.*, 2006). We confirm that our patient also reported severe vomiting and nausea, but considering the seriousness of the infection, this did not lead to discontinuation of the drug, and the patient was supported with the introduction of total parenteral nutrition and anti-emetic therapy. Those side effects disappeared when tigecycline was stopped.

During the past 12 years, colistin has been reintroduced into clinical practice for the treatment of multidrug-resistant bacterial infections, and more recent data do not support the previously reported high incidence of polymyxin-induced nephrotoxicity, showing abnormal renal function in 14–19 % of cases, with higher incidence in patients who had acute or chronic renal impairment at the baseline (Falagas & Kasiakou, 2006). In accordance with these data, our patient, who had normal renal function at the baseline, did not show any sign of nephrotoxicity during the administration of colistin, although it was co-administered with cyclosporin A.

In conclusion, our case suggests that severe infections caused by multiresistant bacteria may require a wider testing of antibiotic sensitivity. This approach disclosed an unexpected sensitivity to tigecycline, permitting a combination therapy, which is preferable in the case of severe infections sustained by multiresistant strains. In addition, our experience confirms that colistin can be used safely in patients with normal renal function. Finally, a multidisciplinary approach combining surgical and medical treatment serves to guarantee an optimal outcome.

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