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BRIEF REPORT

Lung transplantation in two cystic fibrosis patients infected with previously pandrug-resistant *Burkholderia cepacia* complex treated with ceftazidime–avibactam

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Abstract

We describe two cystic fibrosis patients infected with pandrug-resistant *Burkholderia cepacia* complex, with the exception of ceftazidime–avibactam, who received prophylaxis with this antibiotic during lung transplantation. Although both patients had a post-operative relapse of respiratory infection, one with positive blood cultures, ceftazidime–avibactam treatment yielded a favourable outcome. 12 months after transplantation, one patient presented an excellent clinical outcome. However, the other patient died 10 months later due to severe *B. cepacia* sinusitis with intracranial invasion.

Keywords Multi-drug resistance · Respiratory tract infection · Lung transplantation · Cystic fibrosis · Ceftazidime–avibactam · *Burkholderia cepacia complex*

Introduction

Burkholderia cepacia complex (*Bcc*) refers to a group of ubiquitous Gram-negative environmental bacteria found in water, plants, and soil [1]. *Bcc* includes 20 phylogenetically related species [2, 3], with *B. multivorans* and *B. cenocepacia* being the ones most often isolated from patients with cystic fibrosis (CF). These patients may require lung transplantation during the course of the disease, but the decision to perform this procedure in CF patients colonised with *Bcc* is controversial [2]. In fact, *B. cenocepacia* is considered a contraindication for lung transplantation in most centres because of low survival rates and the association of this microorganism with "cepacia syndrome" (necrotising pneumonia with sepsis) [2, 4, 5].

Members of *Bcc* are difficult-to-treat microorganisms due to their multiple drug-resistance mechanisms, such as production of β-lactamases, efflux pump systems, enzymatic modifications, and alteration of drug target sites [1]. The antibiotic strategies used to treat these infections are not based on scientific evidence, instead they depend on local experience [2]. Double or triple antibiotic combinations are often used in the perioperative transplant period [1].

Avibactam is a novel non-β-lactam β-lactamase inhibitor that restores ceftazidime activity against Gram-negative pathogens by inhibiting class A, class C, and some class D β-lactamases [6, 7]. In one study [3], avibactam restored the in vitro activity of ceftazidime in multi-drug-resistant *B. multivorans*, and 90% of non-*B. multivorans Bcc* strains were susceptible to ceftazidime–avibactam, indicating that this approach could be a promising treatment for *Bcc*.

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We report two cases of lung transplantation in CF patients infected with pandrug-resistant *Bcc*, with the exception of ceftazidime–avibactam, treated with this antibiotic.

Patients and methods

Patient 1

A 30-year-old male with CF was chronically infected with *B. cepacia*, as documented by isolation of the microorganism in more than 50% of sputum samples per year. For that reason, he was on regular treatment with nebulized meropenem and received multiple intravenous antibiotics due to pulmonary exacerbations. He was finally accepted for lung transplantation, at which time his predicted forced expiratory volume in the first second (FEV1) was 24% (0.87 L). At that point, the isolated *B. cepacia* strain was resistant to all antibiotics, including all β-lactams, fluoroquinolones, cotrimoxazole, tigecycline, and chloramphenicol. Ceftazidime–avibactam susceptibility testing by gradient MIC strips (bioMérieux) yielded an MIC of 3 μg/mL. Based on these results, we decided not to use ceftazidime–avibactam before lung transplantation to avoid possible development of resistance, and reserve it for prophylaxis during the surgical procedure. Two months later, bilateral lung transplantation was performed. The patient required extracorporeal circulation during 91 min. We administered tailored prophylaxis with 2 g/500 mg ceftazidime–avibactam every 3 h plus 2 g/200 mg amoxicillin–clavulanic acid every 3 h during the surgical procedure. During the first post-operative hours, the patient was hemodynamically unstable and had severe hypoxemia, requiring vasoactive drugs. While he was in the intensive care unit (ICU), tracheal aspirate and blood cultures were positive for *B. cepacia* and resistant to all antibiotics except for ceftazidime–avibactam. We continued treatment with ceftazidime–avibactam 2 g every 8 h. The patient's clinical condition gradually improved and he was discharged from the ICU to the conventional hospitalization ward 12 days later. Ceftazidime–avibactam was stopped 15 days after transplantation. Seven days later, a per-protocol bronchoscopy was performed. *B. cepacia* was isolated in bronchial aspirate and transbronchial biopsy specimens. As there were no signs or symptoms of infection, systemic antibiotics were not administered and nebulized tobramycin was started. The patient was discharged on day 29. 3 months after transplantation, *B. cepacia* was again isolated in bronchoalveolar lavage material from a new bronchoscopy, showing the same MIC to ceftazidime–avibactam (MIC 3 μg/mL). The clonal relation between isolates obtained in pretransplant and post-transplant cultures was investigated by multilocus sequence typing (MLST) [8]. All isolates belonged to sequence type ST-9. The patient was in good clinical condition and his FEV1 value was 2.1 L (60%). Nonetheless, 10 months after transplantation, the patient was admitted with fever and a right earache. Physical examination revealed acute purulent otitis media. An ear swab yielded only *B. cepacia*, with the same susceptibility pattern. We started ceftazidime–avibactam. A computed tomography scan showed severe paranasal sinus disease. Although he also underwent surgical drainage, his condition progressively deteriorated with mastoiditis and petrous bone invasion. Unfortunately, despite 3 weeks of antibiotics (ceftazidime–avibactam + ciprofloxacin + cotrimoxazole) and surgery, the patient died due to intracranial invasion. Of particular note, he had no sinus disease when evaluated as a candidate for lung transplantation.

Patient 2

In a 32-year-old male with CF, *B. multivorans* and methicillin-resistant *Staphylococcus aureus* (MRSA) had been isolated in respiratory samples since 2008. The patient had received several systemic antibiotics (including ceftazidime) during pulmonary exacerbations, and he was on regular treatment with nebulized tobramycin. The last *B. multivorans* strain available before lung transplantation, 40 days before the procedure, was susceptible to gentamicin, tobramycin, doxycycline, and ceftazidime–avibactam (MIC 2 μg/mL). He was accepted for bilateral lung transplantation with a predicted FEV1 of 17% (0.7 L). The procedure was performed with 4 and 6 h of ischemia time for each lung, respectively, and without extracorporeal circulation. Prophylaxis with ceftazidime–avibactam 2 g/500 mg was given every 3 h, plus linezolid 600 mg every 6 h to cover MRSA. *B. multivorans* and MRSA were isolated in bronchial aspirate cultures performed from the explanted lungs. At that point, B. *multivorans* was pandrug-resistant with the exception of ceftazidime–avibactam, for which it showed an MIC of 2 μg/mL. Furthermore, tracheal aspirate culture performed 24 h after lung transplantation due to fever and purulent secretions yielded only *B. multivorans*. The patient was treated with ceftazidime–avibactam as well as nebulised tobramycin for 15 days. His clinical outcome was good and he was discharged from the ICU on day 21 after transplantation. 26 days after transplantation, a per-protocol bronchoscopy was performed, with isolation of *B. multivorans* in both bronchial aspirate and transbronchial biopsy cultures. The microorganism was resistant to all antibiotics tested, but remained susceptible to ceftazidime–avibactam, with an MIC of 2 μg/mL. As the patient showed no signs or symptoms of infection, nebulized tobramycin was the only antibiotic administered. MLST of all *B. multivorans* isolates obtained in pretransplant and post-transplant cultures showed that all belonged to ST-1382. The patient was discharged on postprocedure day 32. 12 months after

transplantation, he was in good clinical condition, did not need hospital admission or systemic antibiotic treatment, and had an FEV1 value of 3.6 L (85%).

Discussion

Here, we describe two patients with cystic fibrosis and pandrug-resistant *Bcc* infection, in whom bilateral lung transplantation could be successfully performed because of *Bcc* susceptibility to ceftazidime–avibactam. Although both patients had *Bcc* infection with positive respiratory cultures in the post-transplant period and one had sepsis and positive blood cultures, they did well by continuing treatment with ceftazidime–avibactam following prophylaxis with the same antibiotic. The response to antibiotic treatment was favourable, but microbiological eradication was not achieved, in line with most previous reports, which had shown persistence of *Bcc* in CF patients [5, 9]. In fact, the CF patient infected with *B. cepacia* finally died 10 months after transplantation due to uncontrollable sinus infection. Nevertheless, the other patient was in good clinical condition at 12 months of follow-up.

Colonization with highly resistant or highly virulent bacteria, fungi, or mycobacteria is considered a relative contraindication for lung transplantation [4]. Specifically, chronic infection with *Bcc* has long been recognized as having a strong negative impact on survival in CF [10]. Unfortunately, these microorganisms are extremely resistant to antibiotics and dramatically increase the post-transplant mortality risk. Some centres consider infection with these organisms a contraindication for transplantation [11]. Colonization with *Bcc* poses a challenge for designing a successful prophylactic strategy to protect the recipient from infection when removing the infected organ, and later, due to persistence of the microorganism in the upper respiratory tract. A multi-drug perioperative antibiotic regimen is used in most centres [1, 2, 5] because of the extensive drug resistance profile of *Bcc*. The susceptibility to ceftazidime–avibactam in this scenario opens a new and promising perspective for treating these patients.

Currently, *B. cenocepacia* accounts for most post-transplant deaths occurring in the lung transplant setting in patients infected with *Bcc* [5, 9, 12, 13]. No difference in outcome has been observed with *B. multivorans* infection [9]. *B. cepacia* is less common, encompassing only 3% of *Bcc* infections in CF patients undergoing lung transplantation [2]. Available data are limited to a report of two cases with poor outcome in the early post-transplant period [14]. Both succumbed after *B. cepacia* infection, with positive blood cultures, 8 and 9 weeks after lung transplantation [14]. It is remarkable that patient 1, whose post-operative blood cultures were positive for *B. cepacia*, had a favourable initial response to ceftazidime–avibactam treatment. However, he died due to progressive sinusitis 10 months later even though ceftazidime–avibactam was restarted and surgery was performed. Only one of seven (14.3%) patients with post-transplant septicaemia due to *B. cenocepacia* survived to hospital discharge in a previous study [5]. However, patients with non-*B. cenocepacia Bcc* infection did not have positive blood cultures and survival was similar to the remaining CF patients. The outcome in patient 1, indicates the importance of local infection source control and suggests that the virulence behaviour of *B. cepacia* may differ from that of *B. multivorans*.

Ceftazidime–avibactam is a novel combination of ceftazidime and a non-β-lactam β-lactamase inhibitor that restores ceftazidime activity against multiple Gram-negative bacteria including *Bcc* [3]. It has been approved by the US Food and Drug Administration (FDA) and by the European Medicines Agency (EMA)for the treatment of complicated urinary tract and intra-abdominal infections, and additionally, for the treatment of hospital-acquired pneumonia based on data from a phase-3 trial (NCT01808092) [15]. Ceftazidime–avibactam concentration in lung epithelial fluid is around 30% [16].

To the best of our knowledge, there are only two cases in which ceftazidime–avibactam was used to treat *Bcc* [17, 18]. A 2-months female infant with prolonged *Bcc* bacteremia (32 days) despite different antibiotic regimens, was successfully treated with ceftazidime–avibactam for 6 weeks for presumed endovascular infection [17]. A CF young adult with *B. multivorans* (only susceptible to ceftazidime–avibactam) and *Pseudomonas aeruginosa* infection was successfully treated with ceftazidime–avibactam and aztreonam [18]. Although they used combination therapy, the authors recognized that clinical response may have been due to ceftazidime–avibactam treatment alone.

As the microorganisms were fully susceptible to ceftazidime–avibactam, our patients were treated with intravenous monotherapy for 15 days (together with nebulised tobramycin in one patient). The optimal duration of antibiotic in this setting is unknown, but we believe that a lengthier antibiotic course is not needed if the patient shows rapid clinical improvement. The development of resistance to ceftazidime–avibactam has been reported in Enterobacteriaceae and *P. aeruginosa* infections [6, 7, 19, 20], and resistance could likely occur in other multi-drug resistant microorganisms such as *Bcc*. Use of ceftazidime–avibactam to treat pulmonary exacerbations in our CF patients could have led to the development of resistance to this new drug before transplantation. As it may be the last line of defence in some *Bcc* infections, we suggest prudent use of ceftazidime–avibactam in this scenario.

This study has some limitations. First, the best antibiotic regimen for *Bcc* infection is unknown, and an in-vitro

synergistic multi-drug combination may have had similar success in these patients. Second, the causal microorganism in both cases was a non-*B. cenocepacia Bcc*; hence, the favourable results obtained with ceftazidime–avibactam may not be applicable to *B. cenocepacia*-infected CF patients undergoing transplantation.

In conclusion, our results suggest that a short course of ceftazidime–avibactam treatment allows successful lung transplantation in CF patients infected with previously pan-drug-resistant *Bcc*. On the other hand, identification of *B. cepacia* may warrant consideration as a relative contraindication for lung transplantation.

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Compliance with ethical standards

Conflict of interest I.L. has been a speaker for Pfizer and has received travel support from Gilead, Merck and Novartis. O.L. has received a research grant from Pfizer and has been speaker for Pfizer, Astellas, Novartis and Merck. The rest of the authors declare that they have no conflicts of interest related to this study.

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