PROCEEDINGS ARTICLE

Antibiotic therapy in hematological neutropenic patients: what is the news?

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Bacterial infection is a very common complication in hematological neutropenic patients whose treatment is extremely challenging for several reasons. First, they are frequently caused by resistant pathogens (multidrug resistant (MDR)), and this may limit the availability of effective therapeutic weapons. Second, these patients often present peculiar pathophysiological conditions that may alter the pharmacokinetic behavior of antimicrobials, and this may explain the need for a new administration schedule and new dosing regimens of antibiotics in this setting. In an era in which there are only few new therapeutic weapons for the treatment of MDR bacterial infections, while advocating for new drugs, what could be effectively done nowadays is to increase the knowledge on appropriateness of the use of currently available drugs to improve clinical outcome and to preserve their activity.

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Bacterial infection is a very common complication in hematological neutropenic patients¹ whose treatment is extremely challenging for several reasons.

First of all, often these infections are caused by resistant pathogens. A recent retrospective analysis of 382 febrile episodes in patients with acute myeloid leukemia showed that the most frequent isolates among the 64% of cases with documented microbiological identification were multidrug-resistant (MDR) Gram-negative bacteria.² Acquisition of MDR Gram-negative bacilli in this setting is frequently related to previous antibiotic therapy,³ and higher mortality rates were observed in cancer patients with bacteremia due to these MDR pathogens.³

The choice of the right antibiotic is usually based on *in vitro* susceptibility data, but this may not be enough for optimal treatment of MDR bacterial infection in leukemia patients.

In fact, another important point is that leukemia patients often present peculiar pathophysiological conditions. They are often hypoalbuminemic and may present glomerular hyperfiltration with augmented renal clearance.^{4,5} All of these mechanisms may alter the pharmacokinetic behavior of most antimicrobial agents and may promote a more rapid elimination of them from the body.⁴ This may explain why the choice of the right dosage of antimicrobials to ensure adequate exposure at the infection site may be very difficult in these patients.

In recent years, the concept of appropriate antibiotic therapy has moved from the idea of selecting the antibiotic only on the basis of its pattern of *in vitro* susceptibility to a more modern concept in which appropriateness must take into account not only this aspect but also the pharmacokinetic–pharmacodynamic behavior of the drug, the site of infection and the patient's pathophysiology.^{6,7}

This is the reason that new administration schedule and new dosing regimens have been recently implemented.

Some antimicrobial agents exhibit time-dependent activity, namely beta-lactams, glycopeptides and oxazolidinones, and this means that the time during which the concentration is maintained

above the minimum inhibitory concentration (MIC) of the pathogen at the infection site is the most relevant determinant of their clinical efficacy.⁸ For this reason, the daily amount of these agents must be refracted in several doses, and it has been shown that administration by means of extended infusion or even better by continuous infusion may improve the probability of optimal exposure and of good clinical outcome with beta-lactams in neutropenic patients.^{9–11} This becomes extremely relevant when treating leukemia patients with infections caused by MDR pathogens with borderline susceptibility, and thus therapeutic drug monitoring (TDM) may be of paramount relevance to optimize drug exposure in these occasions.^{6,12,13} Interestingly, it has been postulated that TDM-guided high-dose continuous infusion of beta-lactams may enable the treatment of MDR *Pseudomonas aeruginosa* infection in immunocompromised patients.¹⁴ In addition, it has been recently suggested that this strategy could even be helpful for the treatment of infections caused by carbapenemase-producing *Klebsiella pneumonia* with carbapenems, provided that this class of agent is administered in combination with another active compound.¹⁵

Conversely, other antimicrobial agents, namely fluoroquinolones, aminoglycosides and lipopeptides, have concentration-dependent bactericidal activity, and this means that the peak (C_{max}) to MIC ratio ($C_{max}:MIC$) and area under the plasma concentration versus time curve (AUC) to MIC ratio are the two most relevant pharmacodynamic determinants of their efficacy.⁸ Accordingly, these agents should be administered once daily with pulse doses whenever feasible, to maximize their level at the infection site.⁶ It is noteworthy that, for example, when using amikacin, it has to be kept in mind that the dosage needed for optimal exposure in patients with acute myeloid leukemia and with hypoalbuminemia should be at least 1.5-fold higher than that needed for the treatment of a standard patient.¹⁶

Among new antimicrobial agents, daptomycin has shown interesting characteristics that may render this drug a valid therapeutic weapon for the treatment of bacteremia due to MDR

Gram-positive bacteria in neutropenic patients. Daptomycin has very rapid bactericidal activity against MRSA¹⁷ and exhibits valid and rapid diffusion into staphylococcal biofilm.¹⁸ These properties may explain why in a recent study assessing efficacy of daptomycin 6 mg/kg once daily for the treatment of Gram-positive catheter-related bloodstream infections in cancer patients it was shown to ensure more rapid symptom resolution in comparison with historical controls treated with vancomycin.¹⁹

In conclusion, in an era in which there are only few new therapeutic weapons for the treatment of MDR bacterial infections, while advocating and waiting for new drugs,²⁰ what could be effectively done nowadays is to increase the knowledge on appropriateness of the use of the currently available drugs to improve clinical outcome and preserve their activity.

CONFLICT OF INTEREST

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