short review

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Clinically relevant infections in hematology and oncology: bacterial infections and the role of novel antibiotics in times of multidrug resistance

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Summary Multidrug resistance of bacterial pathogens is an increasing problem wordwide, especially treatment of multidrug resistant (MDR) gramnegative bacteria is challenging. In the recent past, several new antibiotics as well as new betalactamase inhibitors have been introduced. These novel drugs are valuable new tools for the therapy of infectious complications in cancer patients once there is a high risk for infections due to multidrug-resistant pathogens. While it is necessary to start empirical antibiotic therapy immediately, novel antibiotics only provide benefits in certain situations, depending on the underlying pathogens. Thus, these new antibiotics are best used guided by microbiological testing, since the exact mechanism of resistance determines susceptibility or resistance to certain antibiotics. For empirical therapy, previous culture results and/or colonization with MDR pathogens can help to choose from conventional antibiotics or novel drugs. In clinical practice, optimal antibiotic therapy can be achieved by close collaboration of specialists in hematooncology, infectious diseases and microbiology.

Keywords New antibiotics · Microbiological testing · Multidrug resistance · Bacterial infections · Febrile neutropenia

Abbreviations

BLI	Betalactamase inhibitor
CABP	Community-acquired bacterial pneumonia
cIAI	Complicated intraabdominal infections
CRE	Carbapenem-resistant enterobacteriaceae
cUTI	Complicated urinary infections
ESBL	Extended spectrum betalactamase
HABP	Hospital-acquired bacterial pneumonia
MBL	Metallo-betalactamase
MDR	Multidrug-resistant
MRSA	Methicillin-resistant S. aureus
SSSI	Skin and skin structure infections
TMP/SMX	Trimethoprim-sulfamethoxazole
VABP	Ventilator-associated bacterial pneumonia
VRE	Vancomycin-resistant Enterococcus

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Introduction

Patients with hematologic neoplasias and solid tumors are at increased risk for different kinds of infections due to both common and opportunistic pathogens. The most acute and clinically relevant problem is bacterial infections, which significantly contribute to morbidity and mortality in hemato-oncological patients. In addition, infections lead to delays and/or dose reductions of chemotherapeutics.

For febrile neutropenia, several guidelines have been published that cover all different aspects and provide good advice for the clinical management of this topic [1]. However, the epidemiology of pathogens responsible for bacterial infections is constantly evolving, with multidrug resistance being an increasingly common problem. Much less is known about the best possible treatment of multidrug resistant (MDR) bacteria in cancer patients. While a variety of novel antibiotics and/or combinations of antibiotics with new betalactamase inhibitors have been introduced, these new treatment options are not necessarily better and can even be less effective for the treatment of "standard pathogens". Thus, the aim of this article is to focus on the impact of multidrug

resistance on the management of cancer patients with bacterial infections and discuss possible indications for the most important new antibiotic compounds as well as the putative downsides of novel therapeutics.

Epidemiology

In approximately half of patients with febrile neutropenia, the causative pathogen cannot be identified, so initial antibiotic treatment will often continue to be empirical. In high-risk patients, guidelines usually suggest the use of broad-spectrum betalactams with coverage of enterobacteriaceae, P. aerugiosa, S. aureus and Streptococci as first line agents. Thus, usually piperacillin/tazobactam, group 1 carbapenems (imipenem, meropenem) or pseudomonas-cephalosporins (cefepim, ceftazidim) are chosen as first-line antibiotics [1].

With the emergence of MDR pathogens, there is an increased risk of choosing the wrong initial empirical antibiotic therapy. While historically grampositive cocci have been the most prevalent pathogens in cancer patients, in recent years there has been a shift towards gramnegative bacteria [2]. The most common gramnegative bacteria isolated from bacteremia in patients with cancer are E. coli, P. aeruginosa, K. pneumoniae, Enterobacter spp. and, even more problematic to treat, Acinetobacter spp. and S. maltophilia. Staphylococci are most prevalent among grampositive bacteria, followed by Enterococci [3, 4]. These changes in epidemiology also have implications for treatment options. While there is a rather wide range of antibiotics available for the treatment of resistant grampositive bacteria, the treatment options for certain gramnegative pathogens are much more limited.

In fact, when MDR gramnegative bacilli could be identified as the causative pathogen, a study by Martinez-Nadal found that approximately 40% of neutropenic patients with bacteremia were treated with inappropriate empirical antibiotics, despite choosing treatment regimens suggested by international guidelines. This led to significantly higher mortality, especially in patients that initially presented with pneumonia, shock and with infections due to P. aeruginosa [3].

Problematic pathogens

The World Health Organization has defined a list of priority pathogens that are a major threat to human health due to their resistance profile and the limited availability of effective antibiotics. Many of these bacteria of critical or high priority are typically found as pathogens in patients with febrile neutropenia, i.e. extended spectrum betalactamase (ESBL)-producing or carbapenem-resistant enterobacteriaceae (CRE), carbapenem-resistant P. aeruginosa or Acinetobacter baumannii, as well as grampositive bacteria like methicillin-resistant or vancomycin-resistant S. aureus and vancomycin-resistant E. faecium. Knowledge of local epidemiology is important for the empirical choice of initial antibiotic therapy and whether to try to cover MDR bacteria before getting results from microbiological cultures. Furthermore, some clinical conditions are also correlated with increased incidence of MDR pathogens in neutropenic patients, i.e. duration of neutropenia, presence of indwelling central venous catheters and patient age [5]. To identify patients at risk for infections with MDR pathogens is even more relevant in critically ill patients, since inadequate empirical therapy results in higher mortality [6]. In clinical practice, the highest risk for the wrong choice of empirical therapy in neutropenic patients is given in bacteremia due to S. maltophilia, E. faecium, MDR-P. aeruginosa, coagulase-negative staphylococci and, to a less extent, ESBL E. coli [3].

Extended spectrum betalactamase-expressing pathogens

Infections due to ESBL-producing enterobacteriaceae are an increasingly common clinical problem in patients with chemotherapy-induced febrile neutropenia. At particular high risk are patients with leukemia, hepatobiliary cancer and patients with profound neutropenia [7]. Carbapenems are considered the therapy of choice; in blood stream infections with ESBL-E. coli and K. pneumoniae mortality was lower in patients treated with meropenem compared to piperacillin/tazobactam [8].

Carbapenem-resistant enterobacteriaceae

CRE are of particular concern, as empirical antibiotic therapy with most betalactams will usually fail; targeted therapy will be delayed and only limited effective therapies are available. This leads to high mortality rates, especially in patients with leukemia and prolonged neutropenia. Besides local epidemiology, Lalaoui et al. described a number of risk factors for infections with CRE, namely male sex, middle age, acute leukemia, salvage chemotherapy, neutropenia and bowel colonization with CRE [6]. Microbiological samples with resistance testing are important for guided therapy; the effectiveness of antibiotics with novel betalactamase inhibitors depends on the type of carbapenemase involved [9]. Other treatment options include new tetracycline-derived antibiotics and older drugs like colistin, aminoglycosides and fosfomycin [10].

Nonfermenters

All of the most frequently diagnosed nonfermenters are difficult to treat microorganisms due to their intrinsic resistance to many antibiotics. First line therapy in febrile neutropenia usually consists in pseudomonas-active penicillins, cephalosporins or

carbapenems [1]. Globally, MDR isolates are an increasing problem, in particular strains with efflux pumps or metallobetalactamases. The treatment of MDR pseudomonas should be guided by antimicrobial resistance testing. Possible therapies include antibiotic combinations with new betalactamase inhibtors, aminoglycosides, cefiderocol and colistin [9, 11]. For S. maltophilia, trimethoprim/sulfamethoxazole (TMP/SMX) is considered the therapy of first choice. Depending on microbiological testing, fluoroquinolones can alternatively be used [12, 13]. Among the new drugs, tetracycline derivatives and cefiderocol may be also be effective [9, 11, 14].

A. baumannii is not a frequent cause of infections, but treatment is usually difficult and resistance to carbapenems is rising [15]. Alternative treatment options are new tetracyclins, cefiderocol and colistin [9, 16].

Novel treatment options

In the past few years, a number of new antibiotics have become available; some are combinations of old substances with novel betalactamase inhibitors, others are new members of existing antibiotic classes. The most relevant new additions to the antibiotic armamentarium are listed in Table 1.

Betalactams

Until recently, there have been almost no new drugs against MDR gramnegative bacteria, most commonly MDR enterobacteriaceae. This has changed now by introducing new combinations of betalactams with certain betalactamase inhibitors, some of which have a wider range of activity. In addition, new cephalosporins have been developed. The effectiveness of these drugs largely depends on the kind of betalactamase expressed by pathogens.

Cephalosporins combined with betalactamase inhibitors

Ceftolozan is a new cephalosporin with high activity against pseudomonas combined with an old betalactamase inhibitor (tazobactam), which confers stability against ESBL. On the other hand, ceftazidim is an old pseudomonas cephalosporin combined with a novel betalactamase inhibitor (avibactam). Avibactam accounts for stability against ESBL and certain carbapenemases (KPC, OXA). Both of the new drugs have poor activity against staphylococci, so they should be used carefully unless therapy can be guided by microbiological samples and resistance testing; alternatively they can be combined with an anti-staphylococcal drug. Both drugs have been approved and shown to be effective for the treatment of intraabdominal, urinary and pulmonary infections [17–19].

Table 1 New antibiotics: spectrum of antimicrobial activity, susceptible MDR pathogens and approved clinical indications

Novel antibiotics			
Drug (class)	Relevant pathogens usually covered (among others)	Activity against MDR pathogens	Approved indications
Betalactams			
Ceftolozan/tazobactam (cephalosporin/betalactamase inhibitor)	P. aeruginosa, E. coli, K. pneumoniae, E. cloacae	ESBL, AmpC	cIAI, cUTI, HABP, VABP
Ceftazidim/avibactam (cephalosporin/betalactamase inhibitor)	E. coli, K. pneumoniae, E. cloacae, P. aeruginosa	ESBL, KPC, AmpC, OXA	cIAI, cUTI, HABP, VABP
Ceftobiprole (group 5 cephalosporin)	S. aureus, E. faecalis, P. aeruginosa, E. coli, K. pneumoniae	MRSA	CABP, HABP
Cefiderocol (siderophore cephalosporin)	E. coli, K. pneumoniae, E. cloacae, P. aeruginosa, Stenotrophomonas	ESBL, KPC, MBL, AmpC, OXA	cUTI
Meropenem/vaborbactam (carbapenem/betalactamase inhibitor)	E. coli, K. pneumoniae, E. cloacae, P. aeruginosa	ESBL, KPC, AmpC	cUTI
Imipenem/cilastatin/relebactam (carbapenem/betalactamase inhibitor)	E. coli, K. pneumoniae, E. cloacae, P. aeruginosa	ESBL, KPC, AmpC	cUTI, cIAI
Tetracycline derivatives			
Eravacycline (fluorocycline)	E. coli, K. pneumoniae, E. cloacae, MRSA, E. faecium, Acinetobacter	Most MDR Enterobacteriaceae, MRSA, VRE	cIAI
Fluoroquinolones			
Delafloxacin (fluoroquinolone)	S. aureus, E. coli, K. pneumoniae, E. cloacae, P. aeruginosa, E. faecalis	MRSA	SSSI, CABP

AmpC ampicillinase C, *CABP* Community-acquired bacterial pneumonia, *cIAI* Complicated intraabdominal infections, *cUTI* Complicated urinary infections, *ESBL* Extended spectrum betalactamase, *HABP* Hospital-acquired bacterial pneumonia, *KPC* K. pneumoniae carbapenemase, *MBL* Metallo-betalactamase, *MDR* Multidrug-resistant, *MRSA* Methicillin-resistant S. aureus, *OXA* oxacillinase, *SSSI* Skin and skin structure infections, *VABP* Ventilator-associated bacterial pneumonia, *VRE* Vancomycin-resistant Enterococcus

Combinations of carbapenems with new betalactamase inhibitors

Meropenem/vaborbactam is a combination of a well-known carbapenem with the first boronic acid BLI. Vaborbactam inhibits Ambler class A and class C betalactamases, including KPC carbapenemases. Meropenem/vaborbactam is not active against pathogens with expression of class B (MBL) or class D betalactamases [20]. Similarly, the new BLI relebactam combined with imipenem/cilastatin accounts for stability against class A and class C betalactamases. Imipenem/cilastatin/relebactam is active against most KPC-producing CRE and carbapenem-resistant P. aeruginosa, but not A. baumannii or S. maltophilia [21]. Both new carbapenem-combinations offer an advantage compared to the monodrug only in the case of infections with the relevant MDR pathogens including certain CRE. Common indications are urinary and intraabdominal infections as well as HABP/VABP [22, 23].

Ceftobiprole

Ceftobiprole is a group-5 cephalosporin with activity against grampositive cocci including MRSA and vancomycin-resistant E. faecalis, and gramnegative pathogens including P. aeruginosa. It has been approved for treatment of CABP and HABP, but not for VABP [24].

Cefiderocol

Cefiderocol is a novel siderophore cephalosporin. Siderophores are used by bacteria for iron uptake. Thus, cefidercol exploits this mechanism to actively enter gramnegative bacteria where it exerts its antibiotic effects. The drug is stable against all ambler classes of betalactamases, making it potentially useful for treating infections with various enterobacteriaceae including CRE as well as MDR P. aeruginosa, A. baumannii and S. maltophilia [25, 26].

Other antibiotics

Eravacycline

Eravacycline is a novel fluorocycline, derived from tetracyclines. It has in-vitro activity against a wide spectrum of grampositive and gramnegative bacteria, as well as anaerobes. Eravacyclin is two- to fourfold more potent than tigecycline and is usually active against various MDR pathogens including MRSA, VRE and carbapenemase-producing enterobacteriacea and acinetobacter [16, 27]. P. aeruginosa and Burkholderia are intrinsically resistant. Eravacycline has been shown to be non-inferior to carbapenems for the treatment of complicated intraabdominal infections [28, 29]. As other tetracyclines, eravacycline is a primarily bacteriostatic antibiotic, which should be taken into account when treating severely neutropenic patients.

Delafloxacin

Delafloxacin is a fluoroquinolone with MRSA activity approved for CABP and skin/skin structure infections [30]. Its role in the treatment of febrile neutropenia has not been defined as yet and may be limited in patients that have received fluoroquinolone prophylaxis, and antibiotics from other classes would usually be preferred.

Take home message

In cancer patients with bacterial infections or febrile neutropenia, the risk for infections with MDR pathogens should be assessed before beginning empirical initial antibiotic therapy. Several new antibiotics are available for the treatment of MDR bacteria. For these new drugs knowledge of microbial resistance mechanisms and resistance testing is of pivotal importance for correct treatment choices.

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