There should be no ESKAPE for febrile neutropenic cancer patients: the dearth of effective antibacterial drugs threatens anticancer efficacy

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The success of modern anticancer treatment is a composite function of enhanced efficacy of surgical, radiation and systemic treatment strategies and of our collective clinical abilities in supporting patients through the perils of their cancer journeys. Despite the widespread availability of antibacterial therapies, the threat of community- or healthcare facility-acquired bacterial infection remains a constant risk to patients during this journey. The rising prevalence of colonization by multidrug-resistant (MDR) bacteria in the population, acquired through exposure from endemic environments, antimicrobial stewardship and infection prevention and control strategies notwithstanding, increases the likelihood that such organisms may be the cause of cancer treatment-related infection and the likelihood of antibacterial treatment failure. The high mortality associated with invasive MDR bacterial infection increases the likelihood that many patients may not survive long enough to reap the benefits of enhanced anticancer treatments, thus threatening the societal investment in the cancer journey. Since cancer care providers arguably no longer have, and are unlikely to have in the foreseeable future, the antibacterial tools to reliably rescue patients from harm’s way, the difficult ethical debate over the risks and benefits of anticancer treatments must now be reopened.

Keywords: multi-drug resistance, extended-spectrum β-lactamase, carbapenemase, Gram-negative bacilli, Gram-positive cocci, MRSA, VISA

Introduction

Infection remains a significant cause of excess morbidity and premature mortality among cancer patients receiving potentially curative and life-prolonging antineoplastic treatments. The risks for neutropenic fever syndromes may be categorized as those that are patient related, underlying malignant disease related or treatment related.1 Event rates for neutropenic fever syndromes after cytotoxic chemotherapy vary in different cancer patient populations, with frequencies of 0.9%–1.1% for prostate cancer, 4%–5% for breast cancer, 5%–6% for colorectal cancer, 22%–29% for non-Hodgkin’s lymphoma and 85%–95% for acute leukaemia.1 Invasive bloodstream infection may occur in one in five to one in four of such patients.2,3 Gram-positive and Gram-negative organisms may account for 54%–73% and 26%–45% of these, respectively.2 Strategies of early effective initial empirical antibacterial therapy for neutropenic fevers have reduced all-cause mortality rates from ~21%6 to between 2% and 10%,5,6 depending upon the underlying diagnosis, degree of cancer control, duration of severe neutropenia and type of infection. Changes in the epidemiology of certain bacterial pathogens worldwide, however, threaten to negate the advances made to date.

The challenge of multidrug resistance

Cancer care providers and their patients are facing an unprecedented increase in community- and hospital-based infections due to Gram-positive and Gram-negative pathogens that are resistant to commonly available antibacterial agents.7,8 Examples of such Gram-positive infections include community-acquired pyogenic pneumonia syndromes due to penicillin-resistant Streptococcus pneumoniae,9 acute bacterial skin and skin structure infections due to methicillin-resistant Staphylococcus aureus,10 invasive infections due to heterogeneous vancomycin-intermediate S. aureus (VISA),11 Clostridium difficile-associated diarrhoea syndromes12 and bacteraemia due to vancomycin-resistant Enterococcus spp.13 Of particular concern are the increasing numbers of invasive Gram-negative bacteraemias due to extended-spectrum β-lactamase (ESBL)-producing members of the family Enterobacteriaceae (Escherichia coli, Klebsiella pneumoniae and Enterobacter spp.)14,15 that coexpress resistance to other oral antibacterial agents16 or due to carbapenemase-producing Gram-negative bacilli associated with resistance to all known β-lactam agents, including the extended-spectrum anti-pseudomonal penicillins, cephalosporins, monobactams and...
carbapenems.16 Physicians are struggling to control the tsunami of antibacterial resistance among these Gram-positive and Gram-negative organisms that have ‘learned’ to escape the effects of our antibacterial armamentarium. It is these ‘ESKAPE’ organisms described by Rice17 (Enterococcus faecium, S. aureus, K. pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter spp.) that are responsible for the majority of community- and healthcare facility-associated bacterial infections experienced by patients during their cancer journey.

The rising prevalence of multidrug-resistant (MDR) bacteria in our environment16,18 is increasing the likelihood of exposure of our most fragile and susceptible cancer patient populations to these organisms. For example, prolonged endogenous colonization by carbapenemase-producing blaNDM-1-positive E. coli, possibly community acquired,19 has been observed in cancer patients undergoing treatment.20 The recognition that blaNDM-1-mediated carbapenem resistance was transmitted by plasmids among endogenous intestinal Gram-negative bacteria, remaining ‘hidden’ within the normal enteric microflora, was critical to our understanding of the significance of the threat.18 It has been estimated that >100 million inhabitants of the Indian sub-continent are colonized by blaNDM-1-positive Gram-negative bacilli, enhancing the likelihood that even commonplace infections are potentially untreatable.21 The colonization of cytotoxic therapy-induced damaged intestinal mucosal surfaces by potentially pathogenic bacteria and fungi, together with severe immunosuppression and myelosuppression, increases the risk for translocation across those surfaces, resulting in potentially life-threatening infection.22–25 Factors that promote the spread of MDR pathogens include prolonged or numerous hospitalizations, transfer between hospitals, intensive care unit admission, older age, comorbidities, immunosuppression, prosthetic devices and solid and liquid organ transplantation.26 Antibacterial use is the single most important factor associated with selection for, and colonization by, MDR bacteria.27

Management of infection in cancer patients

Cancer patients who develop invasive infection due to MDR bacteria often experience delays in the initiation of effective antibacterial therapy, which, in turn, may prolong morbidity, with potentially lethal consequences. For example, higher mortality rates (24%–33%) have been observed among non-neutropenic patients with MRSA bloodstream infections associated with higher vancomycin MICs.30 Invasive MRSA infections in febrile neutropenic patients have been associated with even higher mortality rates (>50%) in some centres where these bacteria have become the predominant S. aureus.2,31 Cancer patients with invasive heterogeneous VISA infection have been observed to manifest prolonged fever, persistent bacteraemia and lower serum vancomycin trough concentrations, and to have higher rates of vancomycin treatment failure and prolonged hospitalization.31 Even enhanced dosing of vancomycin may not achieve the desired outcome in cancer patients infected with VISA.32

The 30 day all-cause mortality among haematological malignancy patients with bacteraemia due to ESBL-producing Gram-negative bacilli has been of the order of 25% higher than for those with non-ESBL Gram-negative bacteraemia.33 Mortality rates among neutropenic cancer patients with bacteraemia due to carbapenemase-producing Gram-negative bacilli have been observed to be as high as 69% (95% CI 42%–87%).34 A high environmental prevalence of MDR bacteria enhances the likelihood that the initial empirical antibacterial choice for the treatment of neutropenic fever syndromes will be inappropriate, which itself is independently associated with all-cause mortality.35–38

Increases in morbidity, mortality, duration of hospitalization, incidence of readmission and healthcare costs are linked to the development of antimicrobial resistance among S. aureus, enterococci and Gram-negative bacilli.39,40 MDR bacteria pose a major threat to the successful treatment of patients in almost all branches of medicine, particularly organ transplantation, surgery, dialysis and cancer therapy. This presents cancer care providers with a serious dilemma. Treatment of cancer, and in many cases the cancer itself, increases the risk of infection for patients. The rising prevalence of MDR bacteria and the unavailability of effective antibacterial therapy significantly impair the likelihood of anticancer treatment success. In the absence of effective antibacterial therapy for these MDR bacteria, the only other strategies available to address this dilemma consist of antimicrobial stewardship practices to encourage more disciplined antimicrobial prescribing,21,27 isolation of colonized patients to minimize the nosocomial contact transmission of MDR bacteria and renewed investment in the development of newer and more effective antibacterial agents.7,8,27,41 That said, the pharmaceutical industry appears to be deprioritizing antimicrobial development, citing changing commercial priorities, a difficult regulatory environment and unfavourable assessments by the US FDA and European Medicines Agency.42 Over the next 4 years, global expenditures for oncology drugs are expected to reach US $88 billion and the new oncology drugs in the pipeline outnumber new antibiotics in the pipeline by almost 10 to 1.43

A quarter of a century has passed since the discovery of a novel class of systemic antibacterial agents.44 The Infectious Diseases Society of America, the European Centre for Disease Prevention and Control and the European Medicines Agency have lamented that there are few candidate antimicrobial agents being developed that target the ESKAPE organisms that contribute to the burden of healthcare-associated infections.17,41 For example, antibacterial therapeutic options for the treatment of carbapenemase-producing Gram-negative bacilli are often limited to the administration of tigecycline, with its limited efficacy, or colistimethate, with its significant toxicities.34,45,46 Antimicrobial development has been focused upon improvements to existing molecules, rather than on new agents with novel mechanisms of action.44,47

There is a dearth in the development of antibacterial agents with novel mechanisms of action. As highlighted by Bush,47 many antibacterial agents under development are derived from existing molecular classes (Table 1). The efficacy of these agents for the treatment of neutropenic fever syndromes in cancer patients with high risk for MDR bacterial infection remains unknown.

The rising incidence of MDR infections has been termed a ‘crisis’ by many pundits.8,10,48 The high costs of antibiotic development49 and lower rate of return on the investment42 are disincentives for industry to develop novel antibacterial agents and bring them to market. Further, expensive resource-intensive
Table 1. Examples of antibacterial agents currently under development (based upon data in reference 47)

<table>
<thead>
<tr>
<th>Antibiotic class</th>
<th>Agent</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycoside</td>
<td>plazomicin</td>
<td>broad-spectrum including MDR bacteria</td>
</tr>
<tr>
<td>β-Lactam</td>
<td>ceftobiprole</td>
<td>anti-MRSA cephalosporin</td>
</tr>
<tr>
<td></td>
<td>ceftraroline</td>
<td>anti-MRSA cephalosporin</td>
</tr>
<tr>
<td></td>
<td>avibactam</td>
<td>β-lactamase inhibitor combined with aztreonam, ceftazidime or ceftolozane; inhibits ESBLs or non-metallo-carbapenemases</td>
</tr>
<tr>
<td></td>
<td>BAL 30072</td>
<td>siderophore-bearing monocyclic β-lactam with enhanced uptake into Gram-negative bacteria via iron uptake systems</td>
</tr>
<tr>
<td>Ketolide</td>
<td>cethromycin</td>
<td>active against macrolide-resistant Gram-positive bacteria</td>
</tr>
<tr>
<td></td>
<td>solithromycin</td>
<td>active against macrolide-resistant Gram-positive bacteria</td>
</tr>
<tr>
<td>Oxazolidinone</td>
<td>tedizolid</td>
<td>active against linezolid-resistant staphylococci</td>
</tr>
<tr>
<td></td>
<td>radezolid</td>
<td>active against linezolid-resistant staphylococci</td>
</tr>
<tr>
<td>Quinolone</td>
<td>delafloxacin</td>
<td>active against ciprofloxacin-resistant MRSA</td>
</tr>
<tr>
<td></td>
<td>nemonoxacin</td>
<td>active against ciprofloxacin-resistant MRSA</td>
</tr>
<tr>
<td></td>
<td>JNJ-Q2</td>
<td>active against ciprofloxacin-resistant MRSA</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>omadacycline</td>
<td>broad-spectrum including MDR bacteria</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>TP-434</td>
<td>broad-spectrum including MDR bacteria</td>
</tr>
</tbody>
</table>

MDR, multidrug resistant; MRSA, methicillin-resistant Staphylococcus aureus; ESBL, extended-spectrum β-lactamase.

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non-inferiority trials with large sample sizes have been the basis for antibacterial FDA approval since the 1960s.8,10

Given these considerations, over the last decade changes in the geopolitical approach in response to this crisis have been advocated to encourage industry and academia to invest in new antibacterial research and development as a global moral imperative.10,41,50 The lack of effective antibacterial therapies for the treatment of MDR bacterial infections in susceptible patient groups, such as those undergoing treatment for cancer, threatens to nullify any potential benefits accruable from modern antineoplastic agents.41

Transparency declarations

None to declare.

References


