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Strategies for the empirical management of infection in cancer patients with emphasis on the emergence of resistant gram-negative bacteria

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Abstract

Combinations of antibiotics (namely penicillins and aminoglycosides) have been advocated in the 1970s for the empirical therapy of FN in cancer patients in order to take advantage of the possible synergism between these agents and to extend the potential antimicrobial spectrum of empirical therapy.

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Later, with the development of potent broad spectrum antibiotics, the need for combinations became less obvious as monotherapy with these new agents appeared as effective and less toxic than previously used combinations.

However, today we are facing a major challenge through the emergence of multi-resistant microrganisms. With such bacteria, we might be coming back to the pre-antibiotic era when no active agents were available. This situation is due, in part, by the excessive use of antibiotics, namely as a prophylaxis for infection, and is complicated by the fact that very few new effective antibiotics are being developed by the pharmaceutical industry.

Under these circumstances, it is likely that we will have to resort to "old timers" such as the polymyxins. It is also possible that combination therapy will come back in favor to take advantage of the synergism and extend the spectrum of coverage, just as it has been the case for the management of resistant tuberculosis.

At the same time, the development of multidisciplinary antimicrobial stewardship is mandatory for efficient infection control and minimizing emergence of antimicrobial resistance.

Keywords: Combination; Antibiotics; Aminoglycosides; Beta-lactams; Resistance; Cancer patients; Gram-negative bacteria

1. Introduction

1.1. Febrile neutropenia

Febrile neutropenia (FN), as a major complication of chemotherapy in cancer patients, has been already recognized in the early sixties [1] and has remained the most common complication of cytostatic treatment, still responsible today for serious morbidity, significant mortality and increased cost of therapy [2,3].

Fortunately, several characteristics of FN, that were common in the earlier years, have now changed; namely the frequent association of FN with gram-negative bacteremia, which carried a 90% mortality [4]. Today, FN is associated with gram-negative bacteremia in 7% of the patients and results in a mortality rate of 6–43%, depending on the presence of various risk factors [5].

1.2. Empirical therapy

Because of the distressingly elevated mortality in patients with FN and sepsis, it was recommended to administer antimicrobial therapy to all patients with FN, as soon as fever was present, without waiting for further clinical and/or microbiological demonstration of infection [6]; the so called empirical approach. The value of the concept of empirical therapy for FN has never been verified in a controlled trial comparing therapy based on clinical and microbiological grounds (the orthodox position) and the empirical approach, probably because the latter clearly reduced the high mortality rate associated with FN for which therapy was delayed [7].

Interestingly, in these early studies [6,8], not only the concept of early therapy was being tested, but also these trials used antimicrobial regimens (carbenicillin plus gentamicin) that were actually highly synergistic against many gram-negative bacilli, namely Pseudomonas aeruginosa. These observations paved the road for the use of beta-lactam plus aminoglycosides in patients with FN.

2. Combination therapy

2.1. Rationale

The microbiological justifications for the use of combinations of antimicrobial drugs has been extensively discussed by Jawetz [9] who classified the antibiotics available at that time on the basis of their behavior when used in combination in vitro: indifference, synergism or antagonism. Synergism was recognized to be often present when penicillins were used together with aminoglycosides (streptomycin, at that time) resulting in an increased rate of bactericidal action; then it was hypothesized that antimicrobial synergism might prove particularly helpful for situations in which cure of infection depends on bactericidal action, capable of eradicating microorganisms without significant assistance from host mechanisms, such as bacterial endocarditis and sepsis in the deficient host.

2.2. Achievements

With the introduction of newer antibiotics, during the 1970s (namely cephalotin, carbenicillin and gentamicin) with great potential against gram-negative bacilli, a new impetus was given to the microbiological and clinical research of combination therapy and potential synergism. At that time, we found that the use of combinations that were synergistic in vitro against the offending microorganism (synergy was defined as occurring when the minimal inhibitory concentration of each of the drugs in the combination was one quarter or less of the minimal inhibitory concentration of each drug alone) was associated with a significantly better response to antibacterial therapy than the use of combinations that were not synergistic against the causative agent [10].

We also explored the usefulness of the assay of antibacterial activity in the serum, well recognized as a therapeutic guide for the management of bacterial endocarditis, as a tool for monitoring antimicrobial therapy in patients with cancer, most of whom presented with FN [11]. It was found that a